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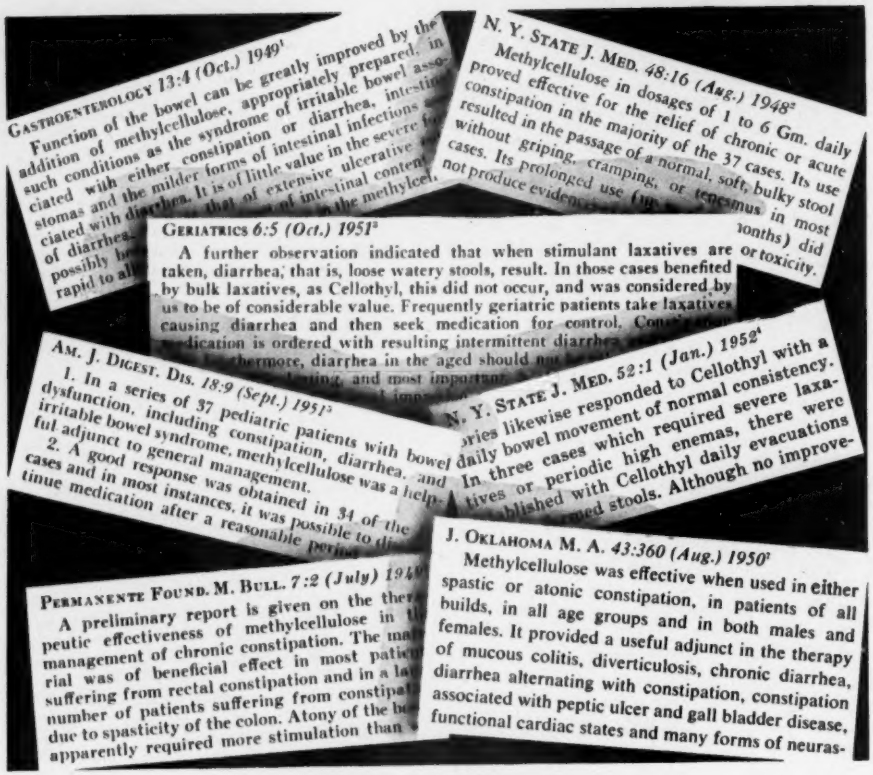

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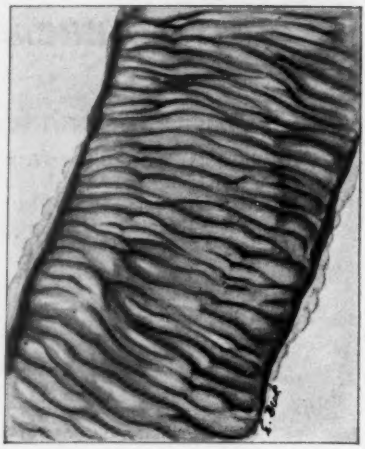

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* Block, L. H.: Management of Constipation with a Refined Psyllium Mucilloid Combined with Dextrose, Am. J. Digest. Dis. 14:64 (Feb.) 1947.

SEARLE RESEARCH IN THE SERVICE OF MEDICINE

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ARCHIVES OF INTERNAL MEDICINE

VOLUME 89 MAY 1952 NUMBER 5

SOME EFFECTS OF CORTISONE ON METABOLIC DISTURBANCE ASSOCIATED WITH RENAL EDEMA

Study of Three Patients

NORMAN M. KEITH, M.D.
MARSCHELLE H. POWER, Ph.D.
GUY W. DAUGHERTY, M.D.
AND
HADDOW M. KEITH, M.D.
ROCHESTER, MINN.

BRIEF reports on the action of cortisone in six of our patients who had renal edema were made last year.[1] On three of these patients we have since completed detailed studies in the metabolic unit of the Mayo Clinic. Our results confirm many of those already reported with both cortisone and corticotropin (ACTH)[2] therapy and add further information. Fortunately, we were able to study the metabolism of the same patient during two episodes of edema and treatment with cortisone. On both occasions we observed numerous chemical changes as the

From the Division of Medicine (Dr. Norman M. Keith, Emeritus Member, and Dr. Daugherty), the Section of Biochemistry (Dr. Power), and the Section of Pediatrics (Dr. Haddow M. Keith), Mayo Clinic.

1. (*a*) Keith, N. M.; Power, M. H., and Daugherty, G. W.: The Action of Cortisone in Nephritis with Edema, Proc. Staff Meet., Mayo Clin. **25**:491-492 (Aug. 16) 1950. (*b*) Keith, N. M.; Power, M. H.; Daugherty, G. W., and Keith, H. M.: Some Effects of Cortisone on the Metabolic Disturbance Associated with Glomerulonephritis with Edema, J. Lab. & Clin. Med. **36**:843-844 (Nov.) 1950.

2. (*a*) Barnett, H. L.; McNamara, H.; McCrory, W.; Forman, C.; Rapoport, M.; Michie, A., and Barbero, G.: The Effects of ACTH and Cortisone on the Nephrotic Syndrome, Am. J. Dis. Child. **80**:519-520 (Sept.) 1950. (*b*) Burnett, C. H.; Greer, M. A.; Burrows, B. A.; Sisson, J. H.; Relman, A. S.; Weinstein, L. A., and Colburn, C. G.: The Effects of Cortisone on the Course of Acute Glomerulonephritis: Report of a Case, New England J. Med. **243**:1028-1032 (Dec. 28) 1950. (*c*) Farnsworth, E. B.: Studies on the Influence of Adrenocorticotrophin in Acute Nephritis, in Simple Nephrosis and in Nephrosis with Azotemia, in Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950, pp. 297-314. (*d*) Farnsworth, E. B., and Dupee, C. F.: Further Studies on the Effects of ACTH in the Nephrotic Syndrome, in Proceedings of the Second Clinical ACTH Conference, Vol. II.: Therapeutics, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1951, pp. 149-155. (*e*) Luetscher, J., Jr., in discussion on Metcoff, J.; Kelsey, W.; Rance, C. P., and Janeway, C. A.: Effects of ACTH on the Pathologic Psysiology and Clinical Course of the Nephrotic Syndrome in Children, in Proceedings of the Second Clinical ACTH Conference, Vol. I: Research, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1951, pp. 148-159. (*f*) Riley, C. M.: Nephrotic Syndrome: Effect of Adrenocorticotrophic Hormone, Pediatrics **7**:457-471 (April) 1951. (*g*) Thorn, G. W.; Merrill, J. P.; Smith, S., III; Roche, M., and Frawley, T. F.: Clinical Studies with ACTH and Cortisone in Renal Disease, Arch. Int. Med. **86**:319-354 (Sept.) 1950.

edema receded and the metabolism improved. The reactions of the patient were variable and confirmed a previous conception that each episode of edema may have unique features. Detailed facts, gained in this way, should lead to a clearer insight into the problem of the individual patient and the appropriate use of cortisone and other beneficial agents in the treatment of the edema of nephritis.

CLINICAL DATA

Our patients sought medical care because of the presence of considerable edema and proteinuria (Table 1). Ophthalmoscopic examination of the ocular fundi and daily estimations of blood pressure throughout the stay of the patients failed to reveal evidence of vascular disease or hypertension. Our first patient to receive cortisone was a woman, Patient B, aged 33 years (Table 1), who on admission had had the syndrome of lipid nephrosis for three and a half months. During her first admission, our study was necessarily a pilot one and in certain respects incomplete. Nonetheless both the clinical and the metabolic results were gratifying and are recorded in Figure 1*A*.[3] After an upper respiratory infection, which developed two

TABLE 1.—*Renal Disease with Edema; Data on Admission**

					Blood					
						Plasma				
Patient	Sex	Age, Yr.	Duration of Illness on Admission, Mo.	Type of Renal Disease	Whole Blood Urea, Mg./100 Cc.	CO_2, mEq./Liter	Cholesterol, Mg./100 Cc.	Serum, Total Protein, Gm./100 Cc.	Urea Clearance,† Cc./Min.	Urine Protein in 24 Hr., Gm.
B	F	33	3½	Lipid nephrosis	18	23	293	3.9	40 ‡	6.75
			6 §		26	30	540	3.2	79 ‖	2.06
M	M	31	3½	Subacute glomerulonephritis	38	31	468	3.6	47 ‖	10.86
K	F	7½	25	Chronic glomerulonephritis	60	19	706	3.6	32 ‡	16.96

* Edema, Grade 2, was present in each patient.
† The estimations of urea clearance were made some days before complete study of the blood.
‡ Standard urea clearance: Urine volume less than 2 cc. per minute.
§ Second admission.
‖ Maximal urea clearance: Urine volume more than 2 cc. per minute.

and a half months after her dismissal, edema recurred, and within two weeks the patient returned to the hospital and presented much the same clinical and metabolic picture as on her initial admission. On this occasion the patient volunteered to undergo a study in our metabolic unit. Our observations included the effects of diet alone and of diet and cortisone therapy.

Patients M and K belong to that group of patients in whom a nephrotic syndrome develops during the course of subacute or chronic glomerulonephritis. In both patients renal insufficiency was demonstrable but did not increase alarmingly during the administration of cortisone. Abdominal paracentesis was found to be necessary both before and after our metabolic study in Patient K. There are cases, however,

3. The studies during this patient's first admission were not carried out in the metabolic unit of the Mayo Clinic but in a private room in the hospital. However, the patient cooperated well in taking both a uniform daily diet and a uniform fluid intake. The diet was low in sodium chloride and high in protein content. The volumes of urine excreted in 24 hours were collected accurately. The results of the study approximate in many respects those obtained under the more rigorous routine of the metabolic unit.

of nephritic edema in which renal insufficiency is considerable, and, on administration of cortisone or corticotropin, azotemia may increase dangerously. We [1a] reported the findings on two such patients who were given cortisone. When cortisone therapy was discontinued, the azotemia diminished. Metcoff and associates [4] reported a fatal outcome in a child with such a condition following the administration of corticotropin.

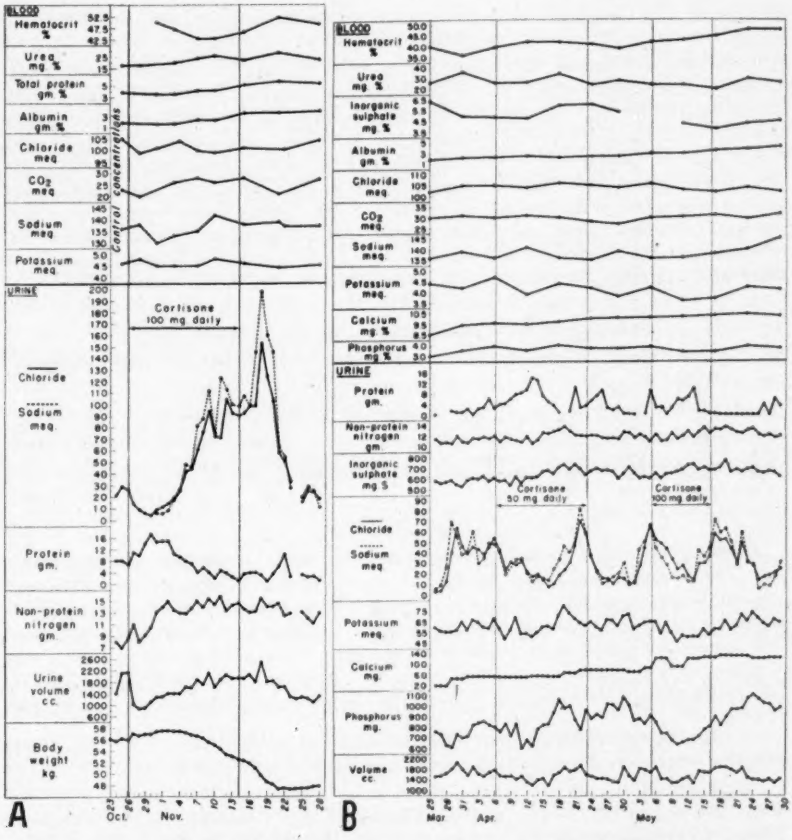

Fig. 1.—*A*, Patient B, first admission: Composite chart of periodic concentrations of several constituents of the blood, 24-hour excretion of certain urinary substances, and daily weight before, during, and after the administration of cortisone. *B*, Patient B, second admission: Composite chart of periodic concentrations of several constituents of the blood, and 24-hour excretion of certain urinary substances before, during, and after two periods of administration of cortisone.

4. Metcoff, J.; Kelsey, W.; Rance, C. P., and Janeway, C. A.: Effects of ACTH on the Pathologic Physiology and Clinical Course of the Nephrotic Syndrome in Children, in Proceedings of the Second Clinical ACTH Conference, Vol. I: Research, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1951, pp. 148-159.

Follow-up data on our three patients indicate that Patient B, 13 months after her second period of treatment, is free from edema and proteinuria. Patient M, after 13 months, has persistent slight edema of his lower legs, proteinuria continues, but there is distinct improvement in the chemical composition of the blood. He is able to carry on his work as a laboratory technician satisfactorily. Reports on Patient K, 10 months after treatment, reveal that her general condition has improved and that the accumulation of ascitic fluid is less rapid than it was.

METHODS OF STUDY

Experience with patients who have nephritic edema has taught us the importance of controlling the daily intake of fluid and food. Our practice has been to give these patients 1,500 to 2,000 cc. of fluid and a weighed diet, adequate in calories, but with small amounts of sodium and chloride and a relatively high content of protein. These dietary conditions were adjusted to the individual patient, and a metabolic balance study in our special metabolic unit of the hospital was carried out[5] (Table 2). Details of the analysis of food and excreta are outlined in a previous article of Sprague and his colleagues.[6] The balance studies were concerned with nitrogen, phosphorus, potassium, sodium, chloride, and calcium levels. Cortisone acetate was administered intramuscularly in a single dose daily in the morning, as a saline suspension of finely ground crystals containing 25 mg. of cortisone acetate in a cubic centimeter.

TABLE 2.—*Daily Content of Weighed and Analyzed Diets*

Patient	Weight on Admission, Kg.	Total Calories	Nitrogen, Gm.	Protein, Gm.	Chloride		Sodium		Potassium		Calcium, Gm.	Phosphorus, Gm.
					Gm.	mEq.	Gm.	mEq.	Gm.	mEq.		
B	52.5	2,240	15.26	95.4	1.02	28.8	0.64	27.8	3.07	78.7	0.67	1.43
M	85.5	2,060	13.67	85.5	1.22	34.4	0.70	30.4	3.24	83.1	0.89	1.37
K	24.2	1,520	9.93	62.0	0.89	25.0	0.51	22.2	2.85	73.1	0.63	1.01

Chemical and Other Methods.[7]—Venous blood for various estimations, including plasma electrolytes, was drawn under oil into a tube containing purified heparin. The corpuscular volume percentage (hematocrit) was determined in graduated tubes after adequate centrifugation; the sedimentation rate was estimated according to the method of Westergren.[8] The sodium and potassium of plasma were estimated in the flame photometer; the carbon dioxide content of plasma was measured by the method of Van Slyke and Neill,[9] and chloride, by a modification of the method of Keys.[10] The blood urea was determined by a modification

5. Miss Gordon Sampson, chief dietitian, Mayo Clinic Metabolism Unit, St. Mary's Hospital, planned and prepared the diets used in metabolic balance studies.

6. Sprague, R. G.; Power, M. H.; Mason, H. L.; Albert, A.; Mathieson, D. R.; Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Observations on the Physiologic Effects of Cortisone and ACTH in Man, Arch. Int. Med. **85**:199-258 (Feb.) 1950.

7. Miss Catherine Ryan, Miss Lenore Rivers, and Mrs. Lucille Adamson, of the Metabolic Section of the Division of Biochemistry, Mayo Clinic, gave technical assistance.

8. Westergren, A.: Studies of Suspension Stability of the Blood in Pulmonary Tuberculosis, Acta med. scandinav. **54**:247-282, 1921.

9. Van Slyke, D. D., and Neill, J. M., cited by Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, Vol. 2, pp. 283-289.

10. Keys, A: The Microdetermination of Chlorides in Biological Materials: Presentation of a Method and an Analysis of Its Use, J. Biol. Chem. **119**:389-403 (July) 1937.

of the urease method of Van Slyke and Cullen [11]; glucose, by the method of Folin and Wu [12]; inorganic sulfate of serum, by the method of Power and Wakefield [13]; inorganic phosphorus, by the method of Gomori [14]; calcium by precipitation as oxalate from ashed plasma. Serum albumin and globulin were estimated by an adaptation of the Kingsley biuret procedure [15]; cholesterol and cholesterol esters, by the methods of Bloor [16] and of Bloor and Knudson [17] respectively; total fatty acids and total lipids, by the methods of Bloor [18]; phospholipids, by a modification of the method of Youngburg and Youngburg.[19] We endeavored to carry out these estimations on the blood approximately once a week.

Sodium and potassium were determined in ashed samples of urine and homogenized specimens of feces by the methods of Butler and Tuthill [20] and Hartzler's [21] modification of the method of Shohl and Bennett; phosphorus, calcium, and inorganic sulfate by methods used with plasma and serum; chloride in urine and homogenized feces was determined by a modified Volhard-Harvey titration. Total protein in the urine was determined as follows: The total nitrogen was determined by the macro-Kjeldahl method. Estimation of the nonprotein nitrogen was performed by the same method after precipitation of the protein with Folin's tungstic acid reagent. Total protein was calculated by subtracting the nonprotein nitrogen value from the total nitrogen value and multiplying by the factor 6.25.

EFFECTS OF CORTISONE ON URINARY EXCRETION

Proteinuria.—With the administration of cortisone to our patients, the excretion of protein by the kidneys varied. In Patients B and M there was an early twofold to threefold increase which persisted for several days and then diminished. This has been the usual sequence of events in the majority of our patients. In both studies of Patient B, as improvement developed the urinary protein decreased to minimal amounts, but Patient M continued to excrete several grams of protein daily (Figs. 1 and 4). The output of protein by Patient K was considerable, continuous, and little influenced by cortisone (Fig. 6). The interesting effect

11. Van Slyke, D. D., and Cullen, G. E.: A Permanent Preparation of Urease, and Its Use in the Determination of Urea, J. Biol. Chem. **19**:211-228, 1914.

12. Folin, O., and Wu, H.: A System of Blood Analysis: A Simplified and Improved Method for Determination of Sugar, J. Biol. Chem. **41**:367-374 (March) 1920.

13. Power, M. H., and Wakefield, E. G.: A Volumetric Benzidine Method for the Determination of Inorganic and Ethereal Sulfate in Serum, J. Biol. Chem. **123**:665-678 (May) 1938.

14. Gomori, G.: A Modification of the Colorimetric Phosphorus Determination for Use with the Photoelectric Colorimeter, J. Lab. & Clin. Med. **27**:955-960 (April) 1942.

15. Kingsley, G. R.: The Direct Biuret Method for the Determination of Serum Proteins as Applied to Photoelectric and Visual Colorimetry, J. Lab. & Clin. Med. **27**:840-845 (March) 1942.

16. Bloor, W. R.: The Determination of Cholesterol in Blood, J. Biol. Chem. **24**:227-231 (March) 1916.

17. Bloor, W. R., and Knudson, A.: The Separate Determination of Cholesterol and Cholesterol Esters in Small Amounts of Blood, J. Biol. Chem. **27**:107-112 (Oct.) 1916.

18. Bloor, W. R.: The Determination of Small Amounts of Lipid in Blood Plasma, J. Biol. Chem. **77**:53-73 (April) 1928.

19. Youngburg, G. E., and Youngburg, M. V.: Phosphorus Metabolism: I. A System of Blood Phosphorus Analysis, J. Lab. & Clin. Med. **16**:158-166 (Nov.) 1930.

20. Butler, A. M., and Tuthill, E.: An Application of the Uranyl Zinc Acetate Method for Determination of Sodium in Biologic Material, J. Biol. Chem. **93**:171-180 (Sept.) 1931.

21. Hartzler, E. R.: Note on Determination of Potassium by Method of Shohl and Bennett, J. Biol. Chem. **122**:19-20 (Dec.) 1937.

of cortisone on the excretion of urinary protein in some nephrotic patients offers an opportunity to investigate further the possible intrarenal or prerenal origin of the protein.[22]

Excretion of Water, Sodium, and Chloride in the Urine.—Initially, after cortisone had been given to both Patients B and M, there was a diminished excretion

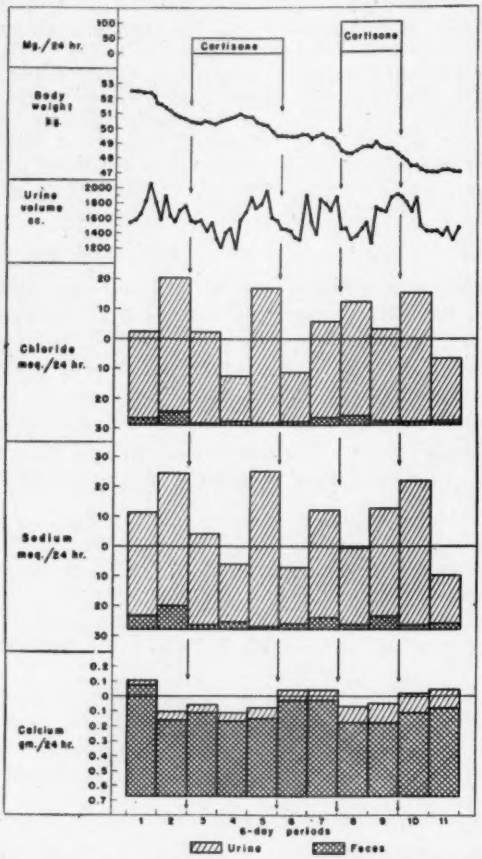

Fig. 2 (Patient B, Second Admission).—Body weight, urine volume, and balance data for chloride, sodium, and calcium. In this and subsequent illustrations showing balance data, the daily intake is charted from the 0 line downward and average daily excretion (fecal below, urinary above) from the bottom line upward. A negative balance is, therefore, indicated by extension of the column above the 0 line, and a positive balance, by a clear area below the 0 line.

of water, sodium, and chloride and at the same time a gain in weight. This period of 7 to 10 days was succeeded by a period of diuresis, with increased excretion

22. Addis, T.; Barrett, E.; Poo, L. G., and Ureen, H.: Prerenal Proteinuria: I. Particle Size, A. M. A. Arch. Int. Med. **88**:337-345 (Sept.) 1951.

of all three constituents and a loss of body weight (Figs. 1, 2, 4, and 5*A*). Patient K when given cortisone continued to excrete a uniform volume of urine, 900 to 1,000 cc. daily, but retained sodium and chloride, and the patient's weight steadily increased. This somewhat anomalous condition was explained by a slow accumulation of ascitic fluid (Figs. 6 and 7*A*).

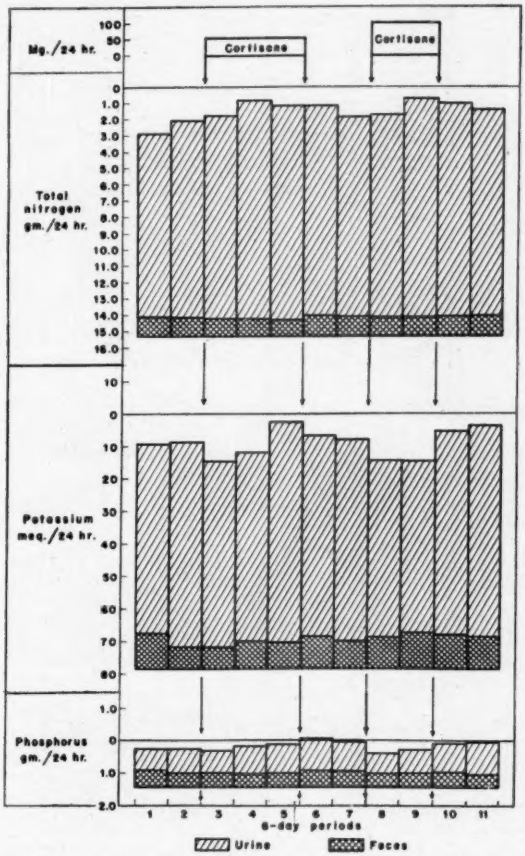

Fig. 3 (Patient B, Second Admission).—Balance data for nitrogen, potassium, and phosphorus.

Excretion of Nonprotein Nitrogen, Potassium, Phosphorus, and Inorganic Sulfate in the Urine.—Previous studies of the action of cortisone suggest that some of its effects are due to an increase in general intracellular metabolism. Results obtained in our present study support this viewpoint. In all three of our patients daily estimations of nonprotein nitrogen in the urine revealed an increased excretion over that in the control period, beginning 5 to 10 days after administration

of cortisone was started and continuing into the postcortisone period. This increase usually occurred later than the increase in proteinuria. Concomitant with this effect on the nonprotein nitrogen there was an increase in the excretion of potassium and phosphorus in Patients B and M (Figs. 1*B* and 4) and of inorganic sulfate in Patients B and K (Figs. 1*B* and 6). Interestingly enough, we some-

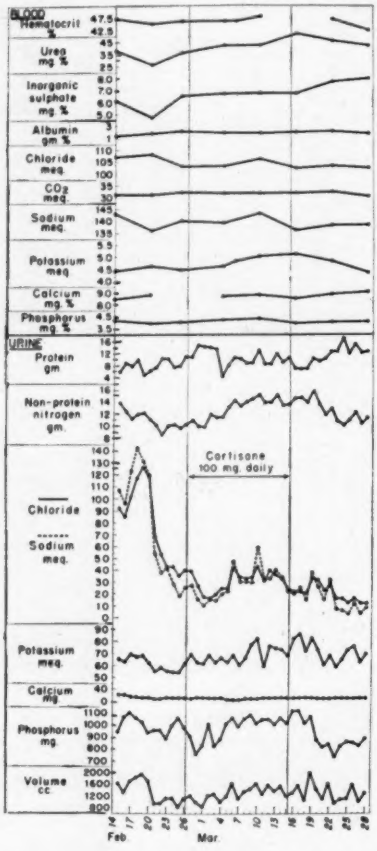

Fig. 4 (Patient M).—Composite chart of periodic concentrations of several constituents of the blood and 24-hour excretion of certain urinary substances before, during and after the administration of cortisone.

times observed a decrease in the excretion of phosphorus and potassium for a few days prior to the initiation of the increased output of these electrolytes (Fig. 1*B*).

Excretion of Calcium in the Urine.—It has been known for 20 years that the excretion of calcium in the urine may be very small in patients who have nephritic

edema.[23] This was evident in our three patients, for during the control periods the excretion of calcium amounted to only 5 to 50 mg. daily (Figs. 1*B*, 4, and 6). It is of interest that with the administration of cortisone to Patient B there was a general improvement in the patient's condition and the excretion of calcium in the

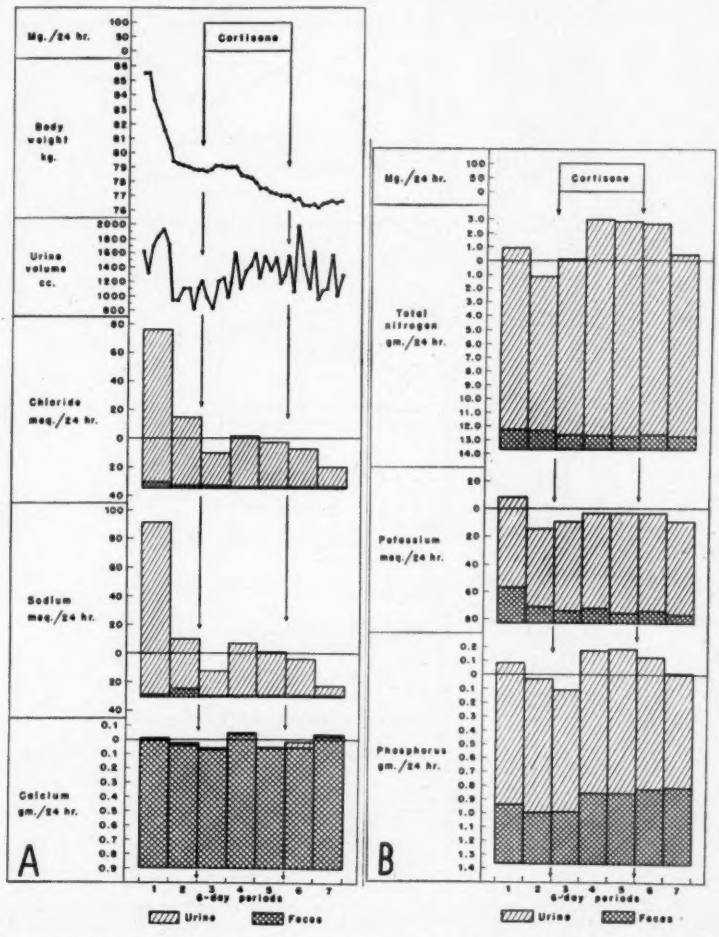

Fig. 5 (Patient M).—*A*, body weight, urine volume, and balance data for chloride, sodium, and calcium. *B*, balance data for nitrogen, potassium, and phosphorus.

23. Albright, F., and Bauer, W.: The Action of Sodium Chloride, Ammonium Chloride, and Sodium Bicarbonate on the Total Acid-Base Balance of a Case of Chronic Nephritis with Edema, J. Clin. Invest. **7**:465-486 (Aug.) 1929. Scriver, W. deM.: Observations on the Excretion of Calcium in 2 Cases of Nephrosis Treated with Parathyroid Extract, ibid. **6**:115-125 (Aug.) 1928.

urine increased to 80 to 125 mg. daily (Fig. 1*B*). In Patients M and K cortisone administration did not alter the initial low excretion of calcium; in fact, the excretion of calcium remained continuously small throughout the metabolic study.

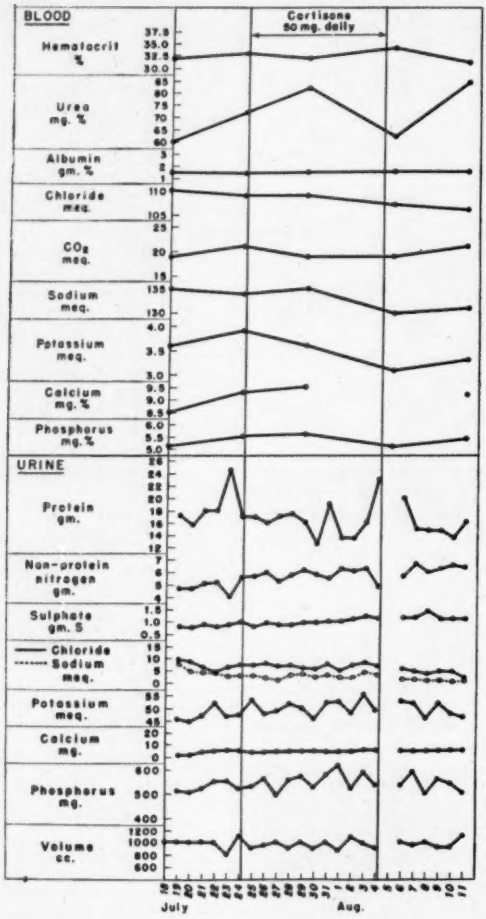

Fig. 6 (Patient K).—Composite chart of periodic concentrations of several constituents of the blood and 24-hour excretion of certain urinary substances before, during, and after the administration of cortisone.

EFFECTS OF CORTISONE ON BLOOD CONSTITUENTS

The weekly estimations of many constituents of the blood revealed significant alterations. In all three patients the initial sedimentation rate was increased to 62 to 119 mm. in one hour, a fact which confirmed the findings on previous studies. Administration of cortisone, on both admissions, to Patient B caused a decrease in

sedimentation rate to normal, but no appreciable change was observed in Patient M. Changes in the corpuscular volume percentage (hematocrit) indicated that cortisone produced small shifts in plasma volume; in some instances an increase, in others a decrease. Possibly more frequent estimations would have revealed a

TABLE 3.—*Lipid Constituents of Blood Plasma*

Date	Patient	Period	Cholesterol, Mg./100 Cc.	Cholesterol Esters, Mg./100 Cc.	Phospholipid, Mg./100 Cc.	Total Fatty Acids, Mg./100 Cc.	Total Lipids, Mg./100 Cc.
10-24-49	B1	Precortisone	293	...	...	...	.....
10-31	..	Cortisone, 100 mg. daily (10-26 to 11-14)	577	...	...	...	.....
11-7	..	.....	494	317	694	867	1,361
11-10	..	.....	430	215	405	1,258	1,688
11-15	..	.....	460	230	510	704	1,164
11-21	..	Postcortisone	300	180	524	520	820
11-28	..	.....	277	157	523	334	611
3-25-50	B2	Precortisone	540	300	410	638	1,178
3-31	..	.....	450	273	438	507	957
4-6	..	.....	468	283	538	600	1,068
4-12	..	Cortisone, 50 mg. daily (4-6 to 4-23)	554	344	584	660	1,214
4-18	..	.....	566	383	554	616	1,182
4-24	..	.....	534	353	584	626	1,160
4-29	..	Postcortisone	467	279	369	630	1,097
5-5	..	.....	420	270	419	516	936
5-11	..	Cortisone, 100 mg. daily (5-5 to 5-16)	450	277	380	490	940
5-17	..	.....	373	210	369	552	925
5-23	..	Postcortisone	305	199	405	670	975
5-29	..	.....	208	167	337	392	685
6-6	..	.....	194	83	335	450	644
2-14-50	M	Precortisone	468	283	538	892	1,360
2-20	..	.....	434	283	618	886	1,320
2-25	..	.....	508	343	484	992	1,500
3-4	..	Cortisone, 100 mg. daily (2-26 to 3-15)	554	343	553	880	1,434
3-10	..	.....	610	420	674	886	1,496
3-16	..	.....	634	390	538	828	1,462
3-22	..	Postcortisone	666	425	636	1,112	1,778
3-28	..	.....	566	353	738	1,062	1,628
8-3	..	.....	577	...	...	818	1,395
11-5	..	.....	666	...	...	1,080	1,746
12-2	..	.....	434	...	...	978	1,412
5-9-51	..	.....	343	...	...	490	833
6-16-50	K	Precortisone	766	...	...	...	.....
.....	..	Cortisone, 50 mg. daily (7-24 to 8-4)	...	...	...	...	.....
8-11	..	Postcortisone	986	...	...	1,382	2,368

more consistent pattern (Figs. 1, 4, and 6). Repeated estimations of glucose in samples of blood withdrawn before breakfast revealed normal concentrations of 66 to 88 mg. in 100 cc. No fluctuations of significance could be attributed to cortisone treatment. The blood urea was definitely increased in all three patients by cortisone therapy, and this increase was accompanied with a rise in serum sulfate in Patients B and M (Figs. 1, 4, and 6). These findings are consistent with the previously reported evidence in patients of increased nitrogen metabolism caused

by cortisone treatment (Sprague and associates [6]) and the rise of blood urea in the nephrectomized rat following administration of cortisone, as observed by Engel.[24]

Serum Protein and Albumin and Plasma Lipids.—With the noticeable clinical improvement in Patient B, there was a gradual rise in the concentration of total

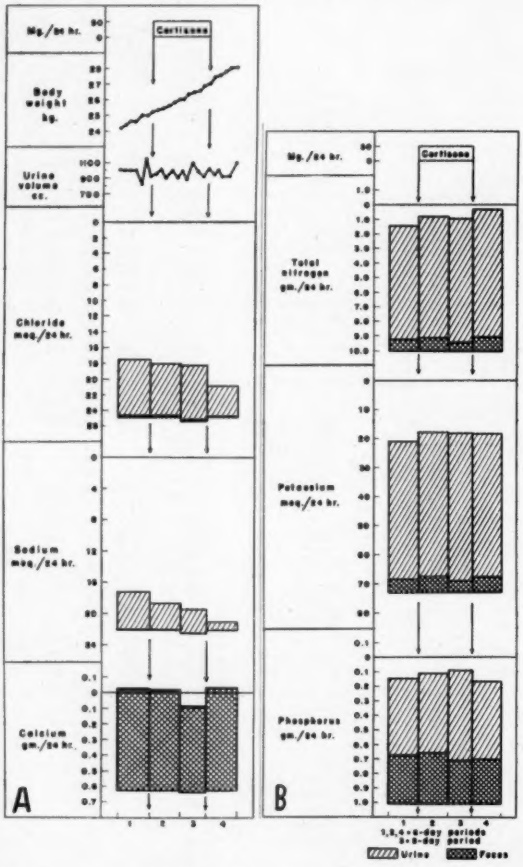

Fig. 7 (Patient K).—*A*, body weight, urine volume, and balance data for chloride, sodium, and calcium. *B*, balance data for nitrogen, potassium, and phosphorus.

protein and of the albumin fraction from their initially low values. In fact, the serum proteins approached normal values on her dismissal (Fig. 1). On the other hand, in Patients M and K cortisone had little effect on the decreased serum

24. Engel, F. L.: Comparative Effects of ACTH and Stress in Nitrogen Metabolism, in Proceedings of the Second Clinical ACTH Conference, Vol. I: Research, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1951, pp. 235-240.

proteins (Figs. 4 and 6). In Patient B, as her condition improved, the lipid constituents of plasma fell, and before her dismissal they approximated normal concentrations. However, in Patients M and K there was no appreciable decrease in plasma lipids due to cortisone while the patients were in the hospital, but in Patient M a year later cholesterol and total lipids were noticeably reduced (Table 3). Farnsworth [2c,d] reported similar variable results in patients given corticotropin. Janeway and associates [25] also noted that there was no consistent alteration in the lipids of the plasma of nephrotic children in whom measles was induced for its diuretic effect.

Inorganic Constituents.—On admission the concentration of chloride in the plasma of our patients was either normal or slightly increased, and shifts during the periods of cortisone administration were minimal. The sodium content was

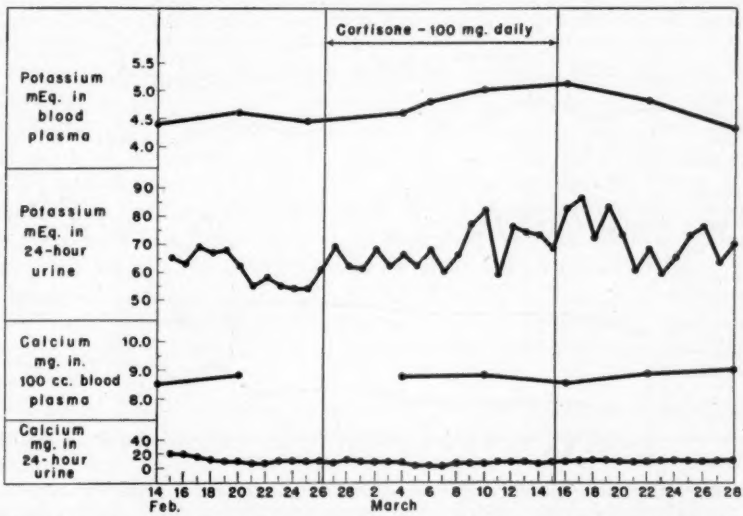

Fig. 8 (Patient M).—Periodic concentrations of potassium and calcium in blood plasma and 24-hour excretion of potassium and calcium in urine. Note during administration of cortisone a concomitant increase in the concentration of potassium in plasma and in the excretion of potassium in the urine. Also note relatively low constant concentration of calcium in plasma and continued small excretion of calcium in urine.

usually normal and fluctuations were small, but in Patients B and K there was a temporary decrease to 130 mEq. while they received cortisone. Shifts in plasma bicarbonate were minimal. A small increase occurred in Patient B (first admission); it was initially high, 32 mEq., in Patient M but was somewhat reduced, 21 mEq., in patient K (Figs. 1, 4, and 6).

Our results with regard to serum potassium were of interest. During the first admission of Patient B, the concentration of potassium was within the normal range

25. Janeway, C. A.; Moll, G. H.; Armstrong, S. H., Jr.; Wallace, W. M.; Hallman, N., and Barness, L. A.: Diuresis in Children with Nephrosis: Comparison of Response to Injection of Normal Human Serum Albumin and to Infection, Particularly Measles, Tr. A. Am. Physicians **61**:108-111 (May) 1948.

throughout and the individual estimations could be considered analytic duplicates (Fig. 1*A*). During the second hospital visit of Patient B and in Patient K the serum potassium distinctly decreased during periods of cortisone administration (Figs. 6 and 9). In contrast, the serum potassium rose when cortisone was given to Patient M but receded after discontinuance of the hormone therapy (Fig. 8). Previously we,[18] and also Luetscher and Deming,[26] reported similar, but greater, increases in serum potassium when cortisone was administered to nephritic patients in whom edema was accompanied with severe renal insufficiency.

A low serum calcium was observed to occur in nephrosis by Salvesen and Linder [27] in 1923 and by others since then. On admission, in our patients, the calcium content of the plasma was reduced to 8.5 mg. in 100 cc. but rose after the giving of cortisone. The increase was greatest in Patient B, in whom plasma calcium finally reached a high normal concentration, 10.4 mg. in 100 cc. (Figs. 8

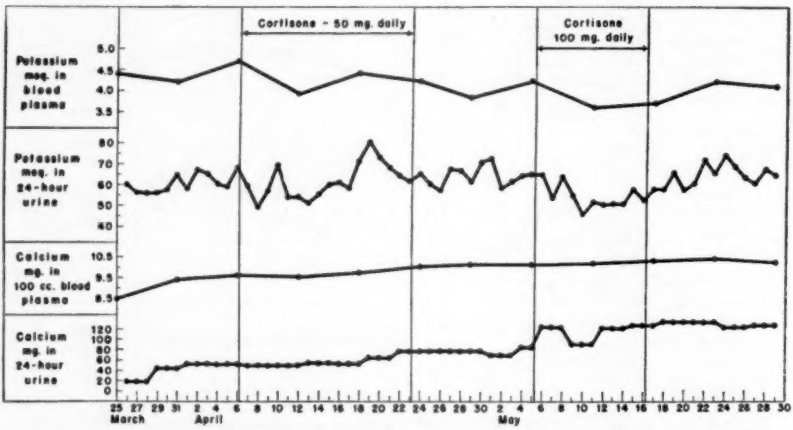

Fig. 9 (Patient B, Second Admission).—Periodic concentrations of potassium and calcium in blood plasma and 24-hour excretion of potassium and calcium in urine. Note during first period of administration of cortisone a decrease in concentration of potassium in plasma concomitant with an increase in excretion of potassium in the urine. Also note slow but progressive increase in both the concentration of calcium in the plasma and its excretion in the urine until normal values are present.

and 9). The concentration of plasma phosphorus was normal and remained unaltered in Patient B throughout her hospital stay. But in Patient M it increased slightly over the normal control value during the administration of cortisone. Patient K revealed a high normal phosphorus content of 5.5 mg. in 100 cc. on admission. It remained unaltered during the administration of cortisone (Fig. 6).

26. Luetscher, J. A., Jr., and Deming, Q. B.: Treatment of Nephrosis with Cortisone, J. Clin. Invest. **29**:1576-1587 (Dec.) 1950.

27. Salvesen, H. A., and Linder, G. C.: Observations on the Inorganic Bases and Phosphates in Relation to the Protein of Blood and Other Body Fluids in Bright's Disease and in Heart Failure, J. Biol. Chem. **58**:617-634 (Dec.) 1923.

RELATION OF CONCENTRATION OF CERTAIN CONSTITUENTS OF BLOOD TO THEIR EXCRETION IN URINE

The simultaneous analysis of certain constituents of blood and urine in our patients has afforded a satisfactory opportunity to study the relation of a given constituent to general metabolism. Previously, in separate paragraphs, we noted that cortisone caused a rise in the concentration of urea in the blood and increased the excretion of nonprotein nitrogen in the urine of our patients (Figs. 1, 4, and 6). It is of interest that these changes occurred simultaneously and that cortisone thus induced increased nitrogen catabolism. This increased flow of nitrogenous waste products from tissue cells into the blood stream and through the kidneys explains the possible danger of administering cortisone to a patient who has renal disease and azotemia. Inorganic sulfate was similarly found to be increased in blood plasma and urine in Patient B (second admission), and the curves for sulfate in serum and output in urine paralleled those for urea and nonprotein nitrogen (Fig. 1*B*).

Interestingly enough, while cortisone caused an increased excretion of potassium in the three patients, B, K, and M, its effect on the concentration in the plasma varied. In patient B this increase in urinary potassium was accompanied with a decrease in plasma content (Fig. 9). Since this patient had relatively satisfactory renal function and similar findings were reported by Sprague and colleagues in cases of rheumatoid arthritis,[6] the decrease in plasma concentration might be considered a normal reaction. However, in Patients K and M definite renal insufficiency was present, and after administration of cortisone the plasma content fell in Patient K but rose in Patient M (Figs. 4, 6, and 8). There is good evidence that the rise in plasma potassium in Patient M could be due to diminished renal function, but the fall in Patient K suggests that there are other controlling factors than the kidneys.

Increased urinary excretion of phosphorus occurred in our patients without significant change in plasma concentration. With regard to calcium, cortisone therapy in Patients M and K altered little the decreased concentration of calcium in plasma and the small excretion in the urine (Figs. 6 and 8). In sharp contrast were the findings of a slowly increasing content of calcium in the plasma and output in the urine in Patient B (second admission), until at the time of her dismissal they both were within normal limits (Fig. 9).

As mentioned previously, the concentration of chloride in blood plasma was normal or slightly increased and remained relatively constant throughout these studies in all three patients (Figs. 1, 4, and 6). This constancy of the chloride level in blood plasma was associated with an initial retention in Patients B and M, but later there was a distinct increase in urinary excretion. In contrast, the high concentration of chloride in the plasma, with but a slight decrease after administration of cortisone, in Patient K was accompanied with progressive retention (Fig. 6). The concentration of sodium in the plasma was persistently constant in Patient B (second admission) and in Patient M. However, cortisone therapy caused a simultaneous decrease in plasma sodium (to 130 mEq.) and in excretion of sodium by the kidneys in Patient B (first admission) and in Patient K. This

retention of sodium was accompanied in both patients with a gain in body weight (Figs. 1*A*, 6, and 7*A*). Similar findings were noted by Metcoff and co-workers [4] in a nephrotic child after the administration of corticotropin.

BALANCE STUDIES

The biochemical changes produced by cortisone therapy indicate that the hormone can stimulate general metabolic reactions. Our balance studies on three patients confirm this viewpoint (Figs. 2, 3, 5, and 7). With regard to sodium and chloride, we found in Patients B and M that the balances of these electrolytes closely paralleled each other. During control periods there was a negative balance, but on administration of cortisone the balance first became positive and later negative. With the positive balance there was a gain in body weight and a decrease in urine volume. After the induction of diuresis, the weight fell and the volume of urine rose. Similar, but less noticeable, changes were observed by Sprague and his colleagues in rheumatoid arthritis.[6] In contrast to Patients B and M, Patient K revealed a positive chloride and sodium balance which progressively increased throughout the metabolic study. The effect of cortisone on calcium balance in our patients was to change a negative balance present during control periods to a positive one.

The balances of nitrogen, phosphorus, and potassium in our patients were positive during at least one of the initial control periods. Grabfield [28] has particularly stressed the presence of a positive balance of nitrogen and sulfur in nephrosis. Cortisone invariably decreased these positive balances either during its administration or immediately after its use was discontinued (Figs. 3, 5*B*, and 7*B*). Cortisone also produced a small, but demonstrable, decrease in the positive balance of nitrogen and phosphorus in Patient K (Fig. 7*B*). But in Patient M, 100 mg. of cortisone given daily induced more marked changes, resulting in a definite negative balance of nitrogen and phosphorus (Fig. 5*B*). It is evident from our balance studies that when cortisone increases tissue metabolism there is not always a uniform liberation of intracellular nitrogen, phosphorus, or potassium.

COMMENT

The chemical disturbances in nephrotic patients are multiple and complex. They include alterations in the metabolism of water and inorganic ions, in protein, in fat, and in the colloid composition of the circulating blood plasma. Eppinger,[29] in 1917, suspecting a hypothyroid factor in nephrosis, reported the beneficial action of thyroid extract in a nephrotic patient. In 1926 Epstein [30] confirmed this finding and advised the giving of relatively large doses of thyroid extract in order that the general metabolism of the patient be distinctly elevated. The therapeutic effects were thought to be due to increased protein catabolism. Cortisone and corticotropin also affect protein metabolism, as repeatedly demonstrated by others and

28. Grabfield, G. P.: Studies on the Nitrogen and Sulphur Metabolism in "Bright's Disease": I. The Retention of Nitrogen and Sulphur in "Nephrosis," J. Clin. Invest. **9**:311-318 (Oct.) 1930.

29. Eppinger, H.: Zur Pathologie und Therapie des menschlichen Ödems, Berlin, Julius Springer, 1917.

30. Epstein, A. A.: Thyroid Therapy and Thyroid Tolerance in Chronic Nephrosis, J. A. M. A. **87**:913-918 (Sept. 18) 1926.

in the present investigation. Our studies clearly reveal that cortisone can cause an increase in the output of nitrogen, sulfate, phosphorus, and potassium, all of which are components of tissue protein. Cortisone also can alter quantitatively the excretion of protein by the kidneys and, in addition, influence fat, water, and ionic metabolism. We have also demonstrated in a single patient, Patient B, that cortisone played a role in restoring to normal a disturbed fat and calcium metabolism. It is significant that cortisone may so influence the water and ionic balance in nephrosis that complete recession of edema occurs. To date there are reports on five patients, including our Patient B, who have apparently made a complete recovery, remaining free from edema and proteinuria.[31] Contrariwise, we wish to point out that Patient K, a 7½-year-old child, when given an adequate dosage of cortisone, revealed a slight increase in protein metabolism, but there was no demonstrable effect on the lipemia or on the edema. This failure of cortisone to influence the lipemia or the edema of some nephrotic patients needs further investigation. Despite the failure of cortisone and corticotropin to influence the edema in stubborn cases of diffuse nephritis, there are many patients in whom the nephrotic syndrome develops, who respond to cortisone or corticotropin treatment with a satisfactory diuresis, and who will remain free from edema for variable periods and even indefinitely.[32]

From time to time individual investigators have suggested that the adrenal cortex may play a role in the pathologic physiology of the nephrotic syndrome. Luetscher[33] recently has demonstrated by a bioassay method an increased excretion of sodium-retaining corticoids in the urine of nephrotic patients. When large changes of these substances occurred, they were reflected by parallel changes in sodium retention and edema. In some patients when diuresis followed the administration of cortisone there was a reduction in the excretion of sodium-retaining corticoids. Luetscher suggested that, in the light of these results, the adrenal cortex may be a causative factor in the development of the nephrotic syndrome, but further study of substances responsible for these findings is indicated before accurate interpretation will be possible.

At this juncture we wish to mention the interesting fact that pediatricians have shown that induction of infection, such as measles, in nephrotic children may bring about a satisfactory diuresis.[34] It is possible that an important factor in initiating diuresis in these children is an increase in general metabolism. This may also apply to the action of nitrogen mustard (methyl-*bis* or *tris* [β-chloroethyl]-amine hydrochloride).[35]

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31. Footnote 2*b*, *e*, and *f*.

32. Footnote 2*d*, *f*, and *g*. Metcoff and others.[4] Luetscher and Deming.[26]

33. (*a*) Luetscher and Deming.[26] (*b*) Luetscher, J. A., Jr.: Effect of Single Injection of Concentrated Human Serum Albumin on Circulating Proteins and Proteinuria in Nephrosis, J. Clin. Invest. **23**:365-371 (May) 1944.

34. Janeway and others.[25] Blumberg, R. W., and Cassady, H. A.: Effect of Measles on the Nephrotic Syndrome, Am. J. Dis. Child. **73**:151-166 (Feb.) 1947.

35. Chasis, H.; Goldring, W., and Baldwin, D. S.: Effect of Febrile Plasma, Typhoid Vaccine and Nitrogen Mustard on Renal Manifestations of Human Glomerulonephritis, Proc. Soc. Exper. Biol. & Med. **71**:565-567 (Aug.) 1949. Taylor, R. D.; Corcoran, A. C., and Page, I. H.: Treatment of the Nephrotic Syndrome with Nitrogen Mustard, J. Lab. & Clin. Med. **36**:996-997 (Dec.) 1950.

There is evidence that cortisone and corticotropin can influence renal function specifically. Their effect on the quantitative excretion of protein in the urine may be due in part to a renal factor.[36] Ingbar and colleagues [37] demonstrated an increase in glomerular filtration rate and tubular function in persons with normal renal function after large doses of cortisone, 600 mg., or corticotropin, 275 to 430 mg., in 24 hours. Kendrick and co-workers [38] reported a small increase in glomerular filtration rate in seven patients receiving cortisone. Heller and associates [39] noted, in an edematous nephritic patient, a rise in glomerular filtration rate from an initially low value to a normal rate after use of cortisone. Metcoff and co-workers [4] and Barnett and colleagues [28] observed after corticotropin therapy in nephrotic children that with diuresis there were increases in the glomerular filtration rate and in the filtration fraction. However, Metcoff and co-workers [4] did not think that the mechanism of corticotropin diuresis in nephrotic children depends on primary sustained alterations in glomerular dynamics.

In our enthusiasm to evaluate new therapeutic agents, such as cortisone and corticotropin, we must not forget that the nephrotic syndrome has been treated beneficially by other agents than those that increase general metabolic activity. Ionic equilibrium has been changed and effective diuresis produced by the administration of such salts as calcium chloride,[40] ammonium chloride,[41] potassium chloride,[42] and potassium nitrate.[43] Ion-exchange resins may alter ionic equilibrium and thus have possible therapeutic value in nephrosis.[44] Successful diuresis

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36. Addis and others.[22] Jameson, E., and Addis, T.: Prerenal Proteinuria: III. Electrophoretic Studies, A. M. A. Arch. Int. Med. **88**:350-355 (Sept.) 1951. Persike, E. C.: Prerenal Proteinuria: II. Observations on Urinary Protein, ibid. **88**:346-349 (Sept.) 1951.

37. Ingbar, S. H.; Kass, E. H.; Burnett, C. H.; Relman, A. S.; Burrows, B. A., and Sisson, J. H.: The Effects of ACTH and Cortisone on the Renal Tubular Transport of Uric Acid, Phosphorus and Electrolytes in Patients with Normal Renal and Adrenal Function, in Proceedings of the Second Clinical ACTH Conference, Vol. I: Research, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1951, pp. 130-137.

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41. Keith, N. M.; Barrier, C. W., and Whelan, M.: The Diuretic Action of Ammonium Chloride and Novasurol in Cases of Nephritis with Edema, J. A. M. A. **85**:799-806 (Sept. 12) 1925.

42. Bassett, S. H.; Elden, C. A., and McCann, W. S.: The Mineral Exchanges of Man: II. Effect of Excess Potassium and of Calcium on 2 Normal Men and on an Oedematous Nephritic, J. Nutrition **5**:1-27 (Jan.) 1932.

43. Keith, N. M., and Binger, M. W.: Diuretic Action of Potassium Salts, J. A. M. A. **105**:1584-1591 (Nov. 16) 1935.

44. Greenman, L.; Peters, J. H.; Mateer, F. M., and Danowski, T. S.: Probable Clinical Utility of Cation Exchange Resins, J. Clin. Invest. **30**:1027-1031 (Sept.) 1951.

has also been produced in nephrosis by administration of xanthine [45] and organic mercury compounds.[46] The action of both types of compounds appears to be chiefly renal. A logical approach to the therapeutic problem in nephrosis was the institution of intravenous injections of hypertonic solutions of sodium chloride, sodium sulfate, mannitol, and sugars, such as dextrose and sucrose. Injection of these solutions increases temporarily the circulating blood volume and output of urine. Their renal action depends on a diminished reabsorption of the glomerular filtrate by the renal tubules. Because of the decreased concentration of serum proteins and particularly of serum albumin in the nephrotic syndrome, the intravenous use of serum proteins seemed preferable to that of hypertonic solutions of certain soluble salts and sugars. With appropriately prepared solutions containing serum and plasma proteins and albumin, satisfactory diuresis occurs in some patients but not in others.[33b] Plasma substitutes, such as solution of acacia,[47] gelatin, and pectin, have also produced effective diuresis in some patients. A common effect of solutions of serum proteins and their substitutes is an increase in circulating blood volume, an increase which is more sustained than that following the injection of simple hypertonic solutions.

There is no doubt among investigators of the nephrosis problem that clinical study has revealed much that is fundamental and necessary for a proper approach to therapy. We have indicated that no single agent has yet been discovered that invariably induces a satisfactory response. The repeated demonstration in nephrotic patients of a wide variability in abnormal chemical composition of the blood and tissues gives support to the viewpoint that the use of various therapeutic agents singly or in combination is sometimes necessary. A good example of this type of therapy is the demonstration by Luetscher and Deming [26] of the effectiveness of serum albumin administration in a number of patients whom cortisone therapy had previously failed to benefit.

SUMMARY

Cortisone is shown to alter general and renal metabolism in the nephrotic patient. These alterations include variable effects on protein, fat, water, and inorganic ions. As a therapeutic agent, it may cause a complete recession of edema or have little effect. Further investigation of patients whose nephrosis is refractory should include studies of the action of other therapeutic agents known to initiate diuresis. If these agents are ineffectual when administered singly, a trial of their effects when combined with cortisone is indicated.

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CHEMICAL BLOCKADE OF THE SYMPATHETIC NERVOUS SYSTEM IN ESSENTIAL HYPERTENSION

Experience with Oral Therapy with 688-A (N-Phenoxyisopropyl-N-Benzyl-β-Chloroethylamine Hydrochloride)

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THE EXACT nature of essential hypertension has not been clearly established, and, as a result, many drugs, diets, and operative procedures have been used in the treatment of this disease. In most instances therapy has either proved more annoying to the patient than the disease itself or produced variable results. The numerous theories regarding the etiological basis of essential hypertension have been summarized repeatedly by many authors,[1] but at present most observers agree that there are probably both neurogenic and humoral factors that produce and maintain blood pressure in certain persons at a hypertensive level. A great deal of the treatment has been aimed at controlling or eliminating the neurogenic factor, for the exact humoral mechanism that operates in hypertension has still not been clarified. Other drugs have been used because of their direct action upon the vascular system.

Therapy with thiocyanate derivatives has been employed for years, and results indicate that marked relief of headache can be achieved with these drugs,[2] but blood-pressure lowering may not be uniformly obtained and toxic reactions are numerous.[3] Veratrum viride has also been used extensively as a hypotensive agent. This agent may produce a marked fall in blood pressure when administered parenterally to

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The 688-A ("dibenzyline") used in this study was supplied by Smith, Kline & French Laboratories, Philadelphia 1.

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2. Alstad, K. S.: The Effects of Thiocyanate on Basal and Supplemental Blood Pressures, Brit. Heart J. **11**:249, 1949.

3. Fischmann, E. J., and Fischman, A.: Thiocyanate in Hypertension: Blood Pressure Behavior After Withdrawal of the Drug, and Serial Electrocardiograms as Criteria of Response, Am. Heart J. **39**:477, 1950.

hypertensive patients, although it does not block or reduce vasopressor responses.[4] The results with oral maintenance therapy have not been completely satisfactory, for tolerance to the drug may develop and severe gastrointestinal symptoms may occur.[5] Nitrites have enjoyed wide popularity in the treatment of hypertension because of their direct vascular action, but the effect produced by these drugs is of short duration, difficult to control, and accompanied with unpleasant side-reactions. Administration of barbiturates is of some value in many hypertensive patients, benefit being obtained because of the sedative action of the drugs.

More recently, agents such as priscoline® (2-benzyl-4, 5-imidazoline hydrochloride),[6] "regitine" (C 7337; 2 [N, *p*-tolyl-N (m′ hydroxyphenyl)-aminoethyl]-imidazoline hydrochloride),[7] and the hydrogenated ergot alkaloids (dihydroergocornine) [8] that have some blocking effect upon the sympathetic nervous system have been used in the treatment of hypertension. Results with these drugs have been variable, and, although they have definite sympathetic blocking properties, their other actions have made it difficult to judge whether adrenergic blockade is the reason for the occasional good results obtained.[9] Dihydroergocornine (D.H.O. 180) administered orally does not appear to have any consistent effect on blood pressure, even when large doses are given.[10] The use of a new ganglionic blocking agent, hexamethonium,[11] and new "antipressor substance," 1-hydrazinophthalazine,[12] is now being investigated,[13] but the exact role of these preparations in the treatment of hypertension has not been established.

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11. Freis, E. D.; Finnerty, F. A., Jr.; Johnson, R. L., and Schnaper, H. W.: Treatment of Severe Hypertension with Hexamethonium, Program of the 24th Scientific Sessions of the American Heart Association, Atlantic City, June 8-9, 1951, p. 47.

12. Schroeder, H. A.: Effects of 1-Hydrazino-Phthalazine in Neurogenic Hypertension, Program of the 24th Scientific Sessions of the American Heart Association, Atlantic City, June 8-9, 1951, p. 10.

13. Schroeder, H. A.: Control of Hypertension by Hexamethonium and 1-Hydrazinophthalazine: Preliminary Observations, A. M. A. Arch. Int. Med. **89**:523 (April) 1952.

A specific sympathetic nervous system blocking agent, dibenamine® (N, N-dibenzyl-β-chloroethylamine hydrochloride), has also been tried in the treatment of hypertension.[14] This agent and its derivatives act peripherally at the neuroeffector junction. They block the action of circulating epinephrine ("adrenolytic" action) and inhibit the response of cells and tissues to sympathetic nervous system stimulation ("sympatholytic" action), i. e., they produce a specific "adrenergic blockade."[15] Slight transient stimulation of the central nervous system has been noted after intravenous injection of dibenamine.®[16] Definite inhibition of cyclopropane-epinephrine-induced ventricular arrhythmias has also been reported,[17] but blockade of the metabolic effects of the sympathicoadrenal system, such as its action on glucose metabolism or its "inhibitory" effects on the gastrointestinal tract, has not been demonstrated.[16] All other effects of dibenamine® are the result of specific blockade of the "excitatory" functions of the sympathetic nervous system. Dibenamine® given intravenously reduces blood pressure and alleviates symptoms of hypertensive encephalopathy[14a]; the sympathetic blockade produced by this agent lasts 36 to 72 hours. Attempts to produce a blockade with oral administration of dibenamine® have been unsuccessful, for the doses required to produce this effect also cause severe nausea and vomiting.

SY 28[18] (N-ethyl-N-[2-bromoethyl]-1-naphthalenemethylamine hydrobromide), which has an action similar to that of dibenamine,® is effective when given

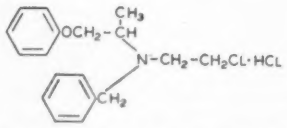

Fig. 1.—Structural formula of 688-A.

orally in animals, but we have thus far been unable to demonstrate a potent sympathetic blocking action or a definite effect on blood pressure in human beings. Further studies with this agent should be undertaken.

A new dibenamine® derivative, 688-A (N-phenoxyisopropyl-N-benzyl-β-chloroethylamine hydrochloride), was recently introduced and was found to be an effective specific sympathetic blocking agent.[19] This drug is more potent and less

14. (a) Wunsch, R. E.; Warnke, R. D., and Myers, G. B.: The Effects of Dibenamine on Severe Hypertension, Ann. Int. Med. **33**:613, 1950. (b) Haimovici, H., and Medinets, H. E.: Effect of Dibenamine on Blood Pressure in Normotensive and Hypertensive Subjects, Proc. Soc. Exper. Biol. & Med. **67**:163, 1948.

15. Nickerson, M.: The Pharmacology of Adrenergic Blockade, J. Pharmacol. & Exper. Therap. **95**:27, 1949.

16. Hecht, H. H., and Anderson, R. B.: The Influence of Dibenamine (N-N-Dibenzyl-β-Chloroethyl-Amine) on Certain Functions of the Sympathetic Nervous System in Man, Am. J. Med. **3**:3, 1947.

17. Nickerson, M.; Smith, S. M., and Goodman, L. S.: The Prevention of Epinephrine-Cyclopropane Cardiac Irregularities in Dogs with Dibenzyl-β-Chloroethyl Amine, Federation Proc. **5**:195, 1946.

18. SY 28 is supplied by Parke, Davis & Company, Detroit 32.

19. McLean, R. A.; Fendrick, A. J.; Macko, E., and Fellows, E. J.: Studies on N-Phenoxyisopropyl-N-Benzyl-Betachloroethylamine: An Orally Effective Adrenergic Blocking Agent, J. Pharmacol. & Exper. Therap. **101**:26, 1951.

toxic than dibenamine,* is effective when given orally in animals, and causes minimal nausea and vomiting.[20] No toxicity related to other systems has been demonstrated. Initial studies in man showed that the drug produced an effective adrenergic blockade that could be maintained by oral medication.[21] No significant gastric symptoms occurred when effective blocking doses were employed, and no other toxic effects were noted. Reactions which were the direct result of sympathetic nervous system blockade included postural tachycardia, drowsiness, and weakness but were rarely incapacitating. The effect of the drug on symptoms and blood pressure in hypertensive patients appeared to indicate that at least a partial "chemical sympathectomy" could be produced and maintained in man by use of 688-A. In view of the results reported above, it was decided that this drug should be further tested in both normal and hypertensive persons, utilizing both an initial oral blocking dose and continuous therapy. The results of studies on normal patients have been reported elsewhere.[22]

MATERIAL AND METHOD

Eleven patients with essential hypertension were selected for study in order to evaluate the effects of continuous adrenergic blockade with 688-A upon symptoms, blood pressure, and sympathetic nervous system activity. The patients had previously been carefully studied in the outpatient department or in the wards of The Mount Sinai Hospital for periods ranging from several weeks to many years. Ten of the patients studied had diastolic blood pressures which were consistently over 110 mm. One patient (T. L.) had early labile hypertension, with a diastolic pressure ranging between 95 and 110 mm. Various forms of therapy had been tried, including sedation, psychotherapy, and salt-poor diet, and in one patient a unilateral sympathectomy had been performed. Therapy had not succeeded in reducing blood pressure significantly or in eliminating symptoms in any of the patients selected. The patients studied were all under 50 years of age. Three were men, and eight were women. Control studies, which included a complete history, physical examination, funduscopic examination, three blood-pressure and pulse-rate recordings in both the recumbent and upright position, a 12-lead electrocardiogram, a ballistocardiogram, a chest roentgenogram, and urine examination, were made in all cases. Cardiac enlargement without evidence of failure was present in five patients, and renal-function studies failed to reveal any renal abnormalities in the patients tested. The test with amobarbital (amytal*) sodium was done on nine patients, and all patients had a cold-pressor test.[23] The presence of an epinephrine-secreting tumor as a cause of the hypertension was ruled out in nine patients by a negative result on the piperoxan test.[24] Digital blood flow studies[25] were performed for seven patients (Dr. Milton Mendlowitz). The patients' conditions were classified

20. Nickerson, M., and Nomaguchi, G. M.: Adrenergic Blocking Action of Phenoxyethyl Analogues of Dibenamine, J. Pharmacol. & Exper. Therap. **101**:379, 1951.

21. Haimovici, H.; Moser, M., and Krankower, H.: The Effect of Oral 688A on Blood Pressure and Pulse Rate in Normotensive and Hypertensive Subjects, Proc. Soc. Exper. Biol. & Med., July, 1951.

22. Moser, M.; Walters, M.; Master, A. M.: Metraux, J., and Taymor, R. C.: Experience with Oral 688 A (N-Phenoxyisopropyl-N-Benzyl-β-Chloroethylamine Hydrochloride): A New Adrenergic Blocking Agent, Proceedings of the National Meeting of the American Federation for Clinical Research, Atlantic City, May 1, 1951.

23. Hines, E. A., Jr., and Brown, G. E.: A Standard Test for Measuring the Variability of Blood Pressure: Its Significance as an Index of the Prehypertensive State, Ann. Int. Med. **7**:209, 1933.

24. Goldenberg, M.; Snyder, C. H., and Aranow, H., Jr.: A New Test for Hypertension Due to Circulating Epinephrine, J. A. M. A. **135**:971 (Dec. 13) 1947.

25. Mendlowitz, M.: The Digital Blood Flow, Arterial Pressure, and Vascular Resistance in Arterial Hypertension and in Coronary Thrombosis, J. Clin. Invest. **21**:539, 1942.

on the basis of the funduscopic study, and all changes were within Grades I to III, according to the criteria of Keith, Wagener, and Barker [26] (Table 1).

In three patients therapy with 688-A was started while they were hospitalized, and two of these were maintained on therapy as outpatients after sympathetic nervous system blockade was established. In the other patient (A. M.), who had had a unilateral sympathectomy, therapy had to be stopped after 10 days because of the patient's lack of cooperation. In the remaining eight patients treatment was started and continued on a clinic basis. They remained ambulatory and continued their routine activities while receiving 688-A. Observations were made daily on the patients who were hospitalized and every other day on the other patients during the first two weeks of the study. After a blockade had been established, the patients were seen once to three times a week. Duration of the observations varied from 4 to 20 weeks. Three blood-pressure and pulse-rate readings were taken in both the recumbent and the upright position during each visit; pupillary size and reaction to light were noted, and the patient was carefully questioned regarding relief of symptoms and side-effects of the drug. The cold-pressor test made with the patient recumbent, ballistocardiograms, and electrocardiograms in the recumbent and upright positions were repeated at frequent intervals, and phenylephrine (neo-synephrine®) hydrochloride was administered intravenously on several occasions to five of the patients to test adrenergic blockade. Breath-holding tests and the Valsalva maneuver (forced expiration with the glottis closed) were also done in four of the patients to judge whether a blockade was present.

The following criteria had to be satisfied before considering that an adrenergic blockade had been established: (1) pupillary constriction, (2) postural tachycardia and/or postural hypotension; (3) partial or complete blockade of the blood-pressure rise during the cold-pressor test; (4) lack of blood-pressure rise or a transient blood-pressure fall when 1.0 mg. of phenylephrine hydrochloride was given intravenously, and (5) blockade of blood-pressure rise after breath-holding for 20 seconds and blockade of blood-pressure "overshoot" following the Valsalva maneuver.

Other useful indications of sympathetic nervous system blockade were lack of sweating and marked nasal stuffiness. In all cases, placebos which resembled the 688-A tablets were given after the completion of the study, and all the observations done initially were repeated.

Five patients first received large single doses of 688-A varying from 2 to 4 mg. per kilogram of body weight until a sympathetic blockade had been established. Blockade was then maintained with doses ranging from 40 to 200 mg. three times a day with meals. Treatment of the remaining six patients was immediately started with divided doses with meals, and they were continued on this regimen. Enteric-coated tablets containing 20 to 40 mg. of 688-A were originally used, but after initial studies revealed irregular absorption in some patients gelatin capsules were employed.

In recording the "control" blood-pressure levels, an average of several readings taken just prior to the administration of 688-A and of all the many readings taken during the patient's hospital and clinic visits during the past three years was used. The range of blood-pressure readings recorded prior to this study was also noted. In nine patients these readings included blood-pressure readings that had been taken after several days of bed rest. The blood-pressure readings taken while the patients were receiving therapy and recorded under the section on results represent the averages of three readings taken in each of two positions (upright and recumbent). Blood-pressure readings were not taken at specific times of the day, and the patient was not rested prior to the determination.

RESULTS

I. *Establishment of an Adrenergic Blockade.*—A blockade of the sympathetic nervous system was established in all patients studied. This blockade was maintained in eight patients with enteric-coated tablets as long as they continued to take the drug and disappeared within 24 hours after treatment with 688-A was stopped.

26. Keith, N. M.; Wagener, H. P., and Barker, N. W.: Some Different Types of Essential Hypertension: Their Course and Prognosis, Am. J. M. Sc. **197**:332, 1939.

TABLE 1.—*Results of Oral 688-A Therapy in Hypertension*

Patient	Age	Sex	Duration of Hypertension, Yr.	Classification, Grade	Blood Pressure on Amobarbital Sodium Test	Digital Blood Flow	Control Blood-Pressure Range		Average Blood Pressure on 688-A Therapy		Blood-Pressure Fall*		Average Postural Tachycardia	Duration of Therapy, Weeks	Dosage, Mg./Day
							Lying	Standing	Lying	Standing	Lying	Standing			
W. D.	44	M	1	II	208/124 to 165/105	Large neurogenic factor; slight fixed resistance	206/120 to 210/130	225/136 to 228/138	176/102	120/82	Av. −32/22 Max. −38/36	−105/55 −128/69	+18	24	120 to 160
S. B.	34	F	8	I	215/125 to 146/100	Large neurogenic factor; slight fixed resistance	200/125 to 230/150	190/128	172/110	145/98	Av. −43/14 Max. −60/19	−45/29 −82/59	+23	20	120 to 200
M. A.	22	F	4	I	180/130 to 140/162	Large neurogenic factor; slight fixed resistance	160/120 to 190/130	178/135	164/118	154/112	Av. −14/6 Max. −24/23	−28/32 −54/53	+20	10	120 to 140
V. A.	46	F	7	I	225/128 to 115/85	Not done	190/110 to 270/145	236/145 to 245/150	163/94	150/94	Av. −77/48 Max. −112/66	−90/56 −121/72	+14	8	120 to 200
T. L.	47	M	?	I	Not done	Not done	150/95 to 160/110	170/116	144/95	122/87	Av. −16/15 Max. −52/36	−48/29 −90/60	+20	6	100 to 120
A. M.†	45	F	8-10	III	195/122 to 145/90	Large neurogenic element; slight fixed resistance	185/110 to 220/130	160/120	182/110	150/102	Av. −13/10	−9/18	+28	10 days‡	
M. R.	42	M	1	II	Not done	Not done	165/110 to 180/110	156/108	155/98	118/82	Av. −10/12 Max. −15/15	−9/18 −50/38	+22	10	80 to 120
N. H.	38	F	9-12	III	No fall in blood pressure	Only slight neurogenic element; large amount of fixed resistance	190/110 to 250/120	194/105 to 206/110	204/116	186/110	Av. +2/6 Max. +20/10	−16/0 −30/8	+12	4	120 to 240
S. S.	46	F	7	III	190/120 to 148/96	Large neurogenic factor; slight increase in fixed resistance	170/115 to 220/160	210/115	172/98	164/94	Av. −38/16 Max. −57/27	−40/23 −60/30	+18	8	360 to 600
M. G.	44	F	11	II	195/115 to 130/88	Large neurogenic element	170/110 to 208/140	190/116	166/110	162/98	Av. −29/10 Max. −56/26	−38/18 −48/30	+12	5	120 to 240
O. W.	40	F	?	II	205/124 to 168/104	Not done	172/110 to 250/156	200/125	185/116	172/108	Av. −15/9 Max. −55/35	−27/18 −102/50	+18	8	220 to 480

* Difference between blood pressure while receiving 688-A and control blood pressures immediately prior to therapy.
† Studied after right thoracolumbar sympathectomy.
‡ Use of drug discontinued because patient refused to cooperate.

In the other three patients blockade was attained but was inconstant, despite continued administration of previously established blocking doses. It was felt that poor absorption of the tablets accounted for the irregular effects in these patients. Evidence of a blockade was usually noted within three to four hours after the administration of a large single dose when the enteric-coated tablets were used, although in two patients the effect was not noted for five or more hours. When the gelatin capsules were used, an effect was noted within one to two hours and was maintained three to six hours. Blockade was more uniformly maintained in the patients who received the gelatin capsules, but the drug had to be given every three to four hours to maintain an effect.

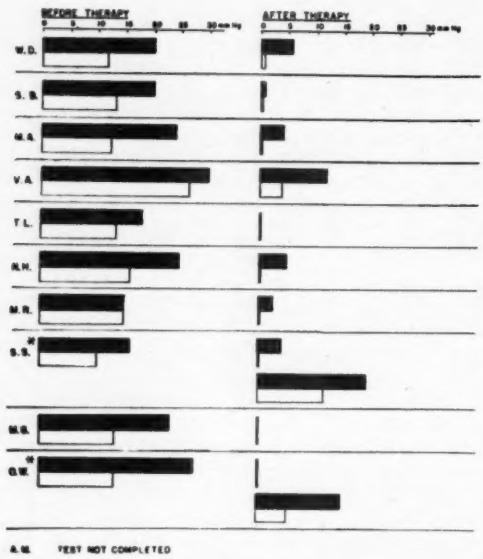

Fig. 2.—Graph showing blockade of blood-pressure rise on cold-pressor test before and after therapy with 688-A. Black columns indicate systolic pressure, and white columns, diastolic pressure. Asterisks indicate patients in whom cold-pressor response was irregularly blocked.

Pupillary constriction was the earliest and most consistently noted effect of the drug. Postural hypotension and postural tachycardia were also noted consistently in 10 of the patients studied. Partial or complete blockade of the blood-pressure rise seen after the cold-pressor test was accomplished in eight patients (Fig. 2). In one patient (A. M.) the test could not be completed because of the patient's severe pain reaction to the cold water. In the other two patients (S. S. and O. W.) the pressor response was occasionally eliminated, but at other times while a patient was receiving therapy a blood-pressure rise similar to that observed before 688-A treatment occurred. The failure to block the cold-pressor response consistently may have been due to irregular absorption of 688-A and the presence of only a "partial" blockade at the time of the testing.

The blood-pressure rise usually noted after breath-holding for 20 seconds [27] or after the Valsalva maneuver was abolished in the four patients who performed these tests. The administration of 1 mg. of phenylephrine hydrochloride intravenously, which usually produces a marked rise in blood-pressure,[28] failed to cause an increase in blood pressure in five patients after 688-A had been given. A transient fall in blood pressure lasting 30 to 60 seconds, followed by a slight rise, actually occurred in three. The results in four of the patients tested with phenylephrine are shown in Figure 3.

II. *Side-Effects and Toxicity* (Table 2).—All the patients studied experienced a "stuffiness" of the nose which was present as long as a blockade was maintained.

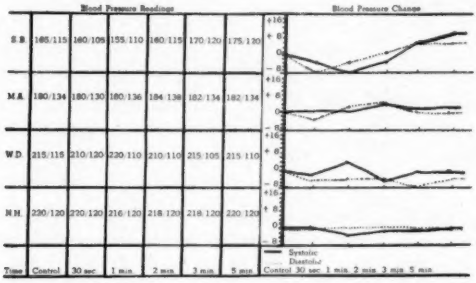

Fig. 3.—Chart showing response of blood pressure to administration of 1 mg. of phenylephrine hydrochloride after 688-A therapy.

TABLE 2.—*Side-Effects and Toxicity*

	Patients No.	Reactions No. with Severe	Comment
Nasal stuffiness	11	2	No sinusitis or infections noted
Dizziness; palpitations	5	1	Coronary insufficiency in one patient; S-T interval depressed on ECG taken in standing position; transient
Gastrointestinal symptoms	4	1	Severe retching and diarrhea in one patient (600 mg./day); 24 hr.
"Weakness"; drowsiness	7	2	Transient, not incapacitating
Irregularity of menstrual cycle	2	..	Delay in onset of menstruation

This symptom proved troublesome in only two patients. Acute sinusitis or upper respiratory infections did not occur in any of the patients studied, despite the fact that the observations were continued during the winter.

Five patients experienced palpitations and marked postural tachycardia and hypotension which caused them varying degrees of discomfort. Most of the patients noted some dizziness and weakness upon arising in the morning, but these annoying symptoms gradually disappeared after the patient had been ambulatory for several hours. Postural tachycardia caused particularly severe discomfort in one patient,

27. Ayman, D., and Goldshine, A. D.: The Breath-Holding Test: A Simple Standard Stimulus of Blood Pressure, Arch. Int. Med. **63**:899 (May) 1939.

28. Keys, A., and Violante, A.: The Cardio-Circulatory Effects in Man of Neo-Synephrine (1-α-Hydroxy-β-Methylamino-3-Hydroxy-Ethylbenzene Hydrochloride), J. Clin. Invest. **21**:1, 1942.

but this was partially relieved by the use of elastic stockings and/or an abdominal binder. The discomfort caused by the postural tachycardia usually decreased after the second week of therapy, although the tachycardia itself persisted in some instances. Three patients experienced transient nausea during the first three days of therapy, and one of them noted nausea, vomiting, and diarrhea of 24 hours' duration when she was given 600 mg. of 688-A daily. These symptoms disappeared when the dosage was decreased. Increase in appetite was noted in three patients. Occasional nausea, but no other gastrointestinal symptoms, was noted by the patients who received the gelatin capsules.

Drowsiness was experienced by seven patients and interfered with the activity of two of them during the first 10 days of treatment. Varying degrees of weakness

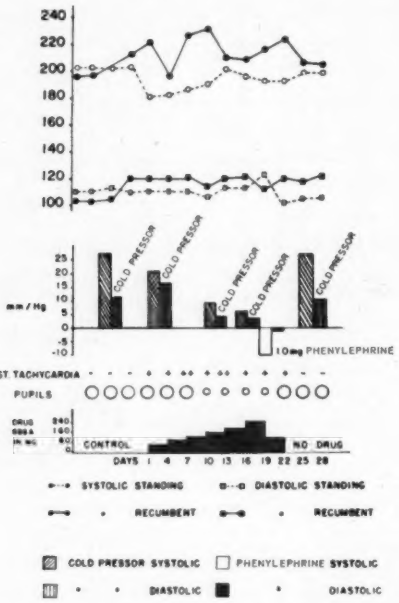

Fig. 4.—Chart showing course on 688-A therapy in Patient N. H., a 38-year-old woman with hypertension of five years' duration. Blood pressure ranged from 190/105 to 250/120. Grade III changes were present. On amobarbital sodium administration the blood pressure fell from 195/112 to 188/108.

were noted in seven patients, and one patient (V. A.) stated that her "mental processes had been slowed up" by the drug. Two patients noted irregularity of menses while receiving therapy, and one of these who had experienced severe dysmenorrhea previously was symptom-free during menstruation while receiving 688-A. The volume of seminal fluid in the two male patients was definitely decreased, but libido, erection, and ejaculation were apparently not altered.

III. *Effects on Blood Pressure, Electrocardiograms, and Symptoms.*—The results obtained in the 11 hypertensive patients studied are tabulated in Table 1. It should be noted that the control blood pressures represent the range of the blood-

pressure readings recorded during many weeks to three years prior to the present study. In 10 of the patients studied, the control blood pressures recorded just prior to the administration of 688-A were significantly higher than the lowest reading listed in Table 1. In judging the blood-pressure-lowering effects of 688-A, however, the final average blood pressure while receiving therapy was compared with the lowest of the previously recorded blood-pressure readings. Evaluation of the results obtained in Patient T. L. is extremely difficult, since this patient had a labile blood pressure and did not show consistent diastolic pressures of 110 mm. or over before therapy was instituted. Despite the fact that a fall in blood pressure was obtained in this patient, he is not being considered as one with a good blood-pressure response to 688-A treatment. Of the remaining 10 patients, five showed an average recumbent diastolic blood pressure while receiving therapy which was significantly lower (12 to 18 mm. Hg) than the lowest previously recorded diastolic pressure. Four other patients showed an average recumbent diastolic pressure fall of between 6 and 10 mm. Hg when compared with the control pressures taken just prior to treatment with 688-A, but this was not considered significant. One patient (N. H.) showed a slight rise in recumbent blood pressure (systolic and diastolic) while receiving the drug.

This patient was a 38-year-old married woman who had had hypertension for about 11 years (Fig. 4). Her blood pressure had ranged from 190/110 to 250/120 and averaged 210/110 in readings taken two days before the beginning of 688-A therapy. Left ventricular enlargement was noted on the chest roentgenogram, and the electrocardiogram showed a pattern indicating left ventricular hypertrophy. Funduscopic examination revealed narrowing of the arterioles with marked arteriovenous nicking and a few scattered hemorrhages and exudates: a Grade III hypertensive retinopathy. Renal-function tests gave normal results, and the results of the piperoxan test were negative for pheochromocytoma. A large element of fixed resistance was demonstrated on digital blood flow studies, and no fall in blood pressure occurred with the amobarbital sodium test. Treatment was started with enteric-coated tablets of 688-A in doses which were gradually increased from 120 to 240 mg. daily. Miosis occurred, and she experienced nasal stuffiness and some postural tachycardia. Her response to the cold-pressor test was blocked. A slight fall in systolic blood pressure occurred after intravenous administration of phenylephrine, further demonstrating an adrenergic blockade. Despite these findings, a blood-pressure rise occurred in the recumbent position while she was receiving therapy, and a significant blood-pressure fall did not take place in the standing position. Blood-pressure lowering was not accomplished in this patient despite the fact that the sympathetic nervous system had been blocked. The patient experienced nausea, weakness, and drowsiness while therapy was being given.

Three patients while receiving 688-A had an average recumbent systolic blood pressure that was 27 to 30 mm. Hg below any previously reported recumbent systolic level. The alterations in recumbent systolic pressures in the other eight patients were not considered significant, although three of these (S. S., M. G., and O. W.) showed an average fall of more than 15 mm. when compared with the most recent control blood-pressure levels.

Nine of the patients had a definite postural hypotension of more than 20 mm. Hg systolic and more than 15 mm. diastolic. Postural changes were not considered of significance in Patient A. M., who had had a previous unilateral sympathectomy, or in Patient N. H. Postural hypotension was more marked immediately after the patient stood up, but in most instances the degree of hypotension was less after the patient had walked about for several minutes. Of the five patients who showed

a good diastolic blood-pressure response to therapy, the ocular changes in three were classified as Grade II, in one as Grade III, and in one as Grade I.

Patients W. D. and S. B. are good examples of patients who were considered to have a satisfactory blood-pressure response to treatment.

W. D. was a 44-year-old man who had experienced severe occipital headaches and "flushes" for one year, and who had a recumbent blood pressure of 206/120 to 210/130 (Fig. 5). On the patient's standing, the pressure rose to 225/135. Some arteriolar nicking was noted on funduscopic examination (Grade II retinopathy), and the chest roentgenogram and electrocardiogram were normal. The results of the piperoxan test were negative, and digital blood flow studies showed a large neurogenic element with some fixed resistance. A blood-pressure fall to 165/105 occurred after administration of amobarbital sodium. The blockade was maintained with administration of 120 mg. of 688-A daily for five weeks. An average blood pressure fall of —32/22 in the recumbent and —105/55 in the standing position was noted with this therapy. The average blood pressure reading during medication was 176/102 recumbent and 120/82 standing. Postural tachycardia, miosis, nasal stuffiness, and a blockade of the blood-pressure response to the cold-pressor test and to phenylephrine given intravenously were obtained. Headaches and "flushes," which had previously occurred, especially after working, were definitely relieved by 688-A

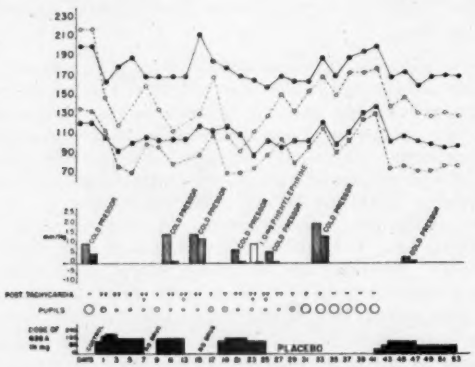

Fig. 5.—Chart showing course on 688-A therapy in Patient W. D., a 44-year-old man with hypertension of one year's duration. Grade I changes were present. Blood pressure ranged from 205/120 to 208/130. On amobarbital sodium administration blood pressure fell from 208/126 to 155/105. Symbols are explained at bottom of Figure 4.

treatment but recurred after placebos were substituted. Use of the drug was restarted after a three-week period of placebo administration, and it has now been administered for an additional 15 weeks with results similar to those obtained during the first five-week study. Dosage has remained the same, and the patient feels well except for occasional "weak spells." Digital blood flow studies done after five months of therapy indicated that a partial release of sympathetic tone had been achieved and maintained. This degree of sympathetic nervous system blockade appeared to be adequate for purposes of lowering blood pressure and preventing rapid rises in pressure following pressor stimuli.

S. B., a 34-year-old woman, had exhibited hypertension after toxemia of pregnancy eight years prior to this study. Her blood pressure ranged from 200/125 to 230/150 and averaged 215/124 just before treatment. Standing blood pressure was 190/128. She had experienced frontal headaches intermittently for two years. Funduscopic examination revealed arteriolar narrowing with arteriovenous nicking: a Grade II hypertensive retinopathy. Left ventricular enlargement was demonstrated on roentgenogram, but the electrocardiogram was normal. Blood pressure was reduced to 146/100 after administration of amobarbital sodium, and digital blood flow studies revealed a large neurogenic element with some slight fixed resistance. Treatment

was started with 160 mg. of 688-A daily while the patient was hospitalized for two weeks, and the medication was continued after her discharge. The dosage was increased to 200 mg. daily on several occasions, and placebos were administered intermittently during the study. Results of blood-pressure readings during the period of observation are shown in Figure 6. The average recumbent blood-pressure fall noted while the patient received therapy was —43/14; in the upright position the fall was —45/29. The averages of the recumbent and upright blood-pressure readings were 172/110 and 145/98, respectively. Nasal stuffiness, postural tachycardia, blockade of the cold-pressor response, and a transient fall in blood pressure after intravenous administration of 10 mg. of phenylephrine were noted. Significant increase in digital blood flow occurred, and flow could not be increased further by the use of tetraethylammonium chloride (5 mg. per kilogram of body weight) and heat while oral therapy with 688-A was maintained. Blood pressure returned to levels approximating pretreatment readings when placebos were substituted for 688-A.

During therapy the patient experienced periods of drowsiness and weakness, expressing an "all-gone" feeling during the first week of therapy. Her condition is at present being maintained

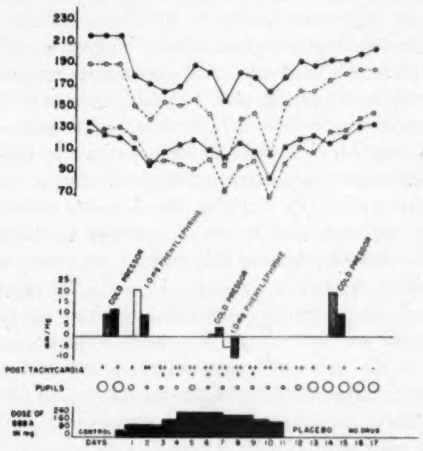

Fig. 6.—Chart showing course on 688-A therapy in Patient S. B., a 34-year-old woman with hypertension of eight years' duration. Grade II changes were present. Blood pressure ranged from 200/130 to 230/150. On amobarbital sodium administration blood pressure fell from 210/124 to 146/100. Symbols are explained at bottom of Figure 4.

satisfactorily with administration of 180 mg. of 688-A daily in gelatin capsule form, and she has noted a definite decrease in troublesome symptoms.

Careful digital blood flow studies done before and after 688-A therapy on Patient M. A. showed that maximum release of sympathetic tone could be achieved with use of this drug. The results closely paralleled those noted with heat and tetraethylammonium chloride given intravenously. Flow studies done after three months of continuous treatment showed that release of sympathetic tone had been maintained.

Three of the patients studied had abnormal resting electrocardiograms, indicating patterns of left ventricular hypertrophy. One of these displayed marked postural tachycardia and hypotension while receiving 688-A. He showed a pattern of coronary insufficiency, i. e., increased S-T depression, when an electrocardiogram was taken in the upright position on the eighth day of therapy. Chest pain was not experienced, and his electrocardiogram improved after the dosage was reduced and

the tachycardia lessened. Ballistocardiograms, which were abnormal for seven patients prior to therapy, returned toward normal in three patients.

Four of the patients studied had experienced occipital headaches and/or "flushes" prior to treatment. In three patients definite symptomatic improvement was noted with 688-A therapy, but in one patient headaches were not improved. One patient complained of extreme nervousness, flushes, and "pressure over the back of the head" after shopping or strenuous housework. These symptoms disappeared while the patient was receiving 688-A and reappeared when placebos were administered.

COMMENT

Since the introduction of surgical sympathectomy as a treatment for hypertension in 1940,[30] numerous workers have compiled data on large series of patients who have been subjected to surgical interruption of the sympathetic nervous system.[31] The most frequently employed surgical procedure which has consistently altered the hypertensive state, at least temporarily, is the thoracolumbar sympathectomy of Smithwick,[32] a supradiaphragmatic and subdiaphragmatic splanchnicectomy producing inconstant results.[33] Smithwick has performed thoracolumbar sympathectomy upon 1,500 patients during the past 10 years, and results of follow-up studies on these patients at present appear to indicate that the procedure has favorably influenced the mortality and survival rates in all hypertensive patients.[34] The results appear to be significant in hypertensive patients with cardiovascular changes, i. e., those classified as Grades II, III, and IV. The lowest mortality rates were noted, however, in patients operated upon before the onset of significant vascular damage, i. e., Grade I. Other observers believe that surgical treatment yields essentially the same results as medical therapy in Grades I, II, and III hypertension and that the operation is indicated only in patients with Grade IV hypertension.[31c] The operation requires a long hospital stay with the accompanying expense, and often sympathetic activity increases in the areas not denervated, i. e., in the upper extremities increased sweating or Raynaud-like phenomena may occur. Postoperative neuralgias are not uncommon, and regeneration of sympathetic nerves may also occur within a short time after operation.[35]

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29. Footnote deleted.

30. (*a*) Allen, E. V., and Adson, A. W.: Treatment of Hypertension: Medical Versus Surgical, Ann. Int. Med. **14**:288, 1940. (*b*) Smithwick, R. H.: A Technique for Splanchnic Resection for Hypertension: Preliminary Report, Surgery **7**:1, 1940.

31. (*a*) Peet, M. M., and Isberg, E. M.: The Surgical Treatment of Arterial Hypertension, J. A. M. A. **130**:467 (Feb. 23) 1946. (*b*) Smithwick, R. H.: Continued Hypertension: Prognosis for Surgically Treated Patients, Brit. M. J. **2**:237, 1948. (*c*) Thorpe, J. J.; Welch, W. J., and Poindexter, C. A.: Bilateral Thoracolumbar Sympathectomy for Hypertension: A Study of 500 Cases, Am. J. Med. **9**:500, 1950.

32. Smithwick.[30b] Thorpe and others.[31c]

33. Grimson, K. S.: The Surgical Treatment of Hypertension, Advances Int. Med. **2**:173, 1947.

34. Smithwick, R. H.: The Effect of Sympathectomy upon the Mortality and Survival Rates of Patients with Hypertensive Cardiovascular Disease, in Hypertension: A Symposium, edited by E. T. Bell, Minneapolis, University of Minnesota Press, 1951, p. 429.

35. Linton, R. R.; Moor, F. D.; Simeone, F. A.; Welch, C. E., and White, J. E.: Thoracolumbar Sympathectomy for Hypertension: Improvements in Paravertebral and Transpleural Routes to Facilitate Extensive Neurectomy, S. Clin. North America **27**:1178, 1947.

If a sympathetic nervous system blockade could be established and maintained by drug therapy, the need for surgical sympathectomy with its accompanying morbidity and mortality would be decreased. The "sympathectomy" would be reversible, and the extent of the blockade could be controlled on a day-to-day basis if necessary. It appears from preliminary studies that 688-A is an orally effective sympathetic blocking agent whose action can be maintained. In its original form, i. e., enteric-coated tablets, absorption and effect were irregularly maintained, and results were not consistent. The presently available gelatin capsules appear to provide more uniform absorption, and a continuous adrenergic blockade can be maintained with no increase in toxicity. The "sympathectomy" produced by 688-A appears to be complete enough to decrease or eliminate the wide fluctuations in blood pressure that ordinarily result from various pressor stimuli, such as cold, or the injection of sympathomimetic drugs, such as phenylephrine. Postural hypotension and the lowering of blood pressure during activity can also be accomplished by this therapy.

It is agreed by most authors that the lowering of blood pressure and the prevention of wide blood-pressure swings or sudden increases of blood pressure to high levels are beneficial to the hypertensive patient and postpone the development of progressive cardiac disease.[36] The development of renal disease and cerebral accidents may also be delayed. Some authors [33] believe that it is more important to stabilize and produce a fall in blood pressure while patients are in the upright position and while they are ambulatory or at work than to lower the patient's pressure in the recumbent position. Definite benefit to the hypertensive patient results if these blood-pressure changes are maintained over a long period.

The blood-pressure effects of any drug or procedure are extremely difficult to evaluate in view of the generally recognized wide fluctuations in blood pressure observed in the same patient from time to time.[37] Systolic pressure determinations are notoriously variable. For this reason the lowest of all the previously recorded blood-pressure readings, and not the average or mean pressure, was used as the base line on which to judge the effects of 688-A therapy, even if the lowest reading had been recorded many months before treatment with this drug. The diastolic blood-pressure changes alone were considered significant. The effects of bed rest and sedation on blood pressure are also well known and must be taken into consideration before any conclusions may be drawn in any study of blood pressure.[38] In order to eliminate these factors in all the patients administration of sedatives was discontinued, and the patients remained ambulatory while being studied. They were not rested prior to pressure determinations, either before or during 688-A therapy.

With these variables considered, the results in five patients who experienced a sustained fall of diastolic blood pressure to 12 to 18 mm. Hg lower than the lowest previously recorded diastolic pressure in the recumbent position appear to indicate

36. Nickerson.[9] Smithwick.[31b]

37. Perera, G. A.: Diagnosis and Natural History of Hypertensive Vascular Disease, Am. J. Med. **4**:416, 1948.

38. Watkin, D. M.; Froeb, H. F.; Hatch, F. T., and Gutman, A. B.: Effects of Diet in Essential Hypertension: I. Baseline Study: Effects in 86 Cases of Prolonged Hospitalization on Regular Hospital Diet, Am. J. Med. **9**:428, 1950.

a satisfactory blood-pressure response. Nine of the 11 patients studied, however, showed a constant diastolic pressure fall of 18 to 55 mm. Hg in the upright position. In most instances the readings in this position actually were 30 to 60 mm. Hg lower than the more recent control diastolic pressure levels. The marked postural hypotension noted in these patients compares favorably with the postural effects of surgical sympathectomy.

None of the patients studied, however, was followed for a long enough period to state whether the blood-pressure fall could be permanently maintained. Minimal tolerance appeared to develop in several patients, but blockade could be maintained by increasing the dosage of 688-A. Vascular tone, as measured by digital blood flow studies, demonstrated release of sympathetic tone in the patients tested, and additional follow-up studies will be done to determine the duration of this effect.

Physiological side-reactions, such as orthostatic hypotension and tachycardia, usually observed after surgical sympathectomy, were also noted in the patients treated with 688-A, but these side-effects did not preclude further use of the drug in any case. The fact that the discomfort caused by postural effects appeared to decrease after the first 10 days to two weeks of therapy suggests some vascular readjustment to sympathetic blockade. The marked nasal stuffiness seen after 688-A administration is not noted after thoracolumbar sympathectomy and may prove to be a source of great discomfort in some patients, although this was not noted in our series. The extreme weakness and drowsiness observed during the first week or two of therapy in several of our patients suggests that therapy should be initiated with smaller doses.

It is hoped that the effects of this new drug will be tested in larger groups of patients in order to determine its place in the treatment of hypertension. If its effects can be maintained, its use may prove to be as valuable in certain groups of hypertensive patients as surgical sympathectomy has been, without the drawbacks of a surgical procedure. If the effect proves to be transient or tolerance develops, 688-A might possibly be used to predict the effects of surgical sympathectomy. Cases are now being studied to judge whether the drug can be used in this manner.

The effect of 688-A therapy on menstrual irregularities and uterine pain should be more thoroughly investigated. Decrease in uterine pain during both labor and menstruation has been reported after sympathetic resection of the second lumbar nerve bilaterally in human beings,[39] and definite improvement in dysmenorrhea was noted in one of our patients. If this effect can be obtained with oral administration of 688-A, the drug may prove to be of value in the treatment of this condition. The usefulness of this drug in the treatment of peripheral vascular disease and Raynaud's phenomenon should also be studied.

SUMMARY

An adrenergic blockade was established and maintained by oral medication with a new sympathetic blocking agent, 688-A (N-phenoxyisopropyl-N-benzyl-β-chloroethylamine hydrochloride), in 11 patients with essential hypertension. Blockade was irregular when enteric-coated tablets were used but was continuous when gelatin capsules were substituted. Dosage varied from 1 to 4 mg. per kilogram of body weight per day and was less with the latter preparation.

39. Smithwick, R. H.: Personal communication to the authors.

A significant fall in recumbent diastolic pressure was obtained in 5 of the 11 patients. Significant lowering of diastolic blood pressure in the upright position occurred in 9 of the 11 patients. Recumbent and postural effects on the blood pressure and the cold-pressor response in hypertensive patients seem to compare favorably with results obtained in patients subjected to surgical sympathectomy.

Severe toxic reactions did not occur, but side-effects, such as weakness, drowsiness, nasal stuffiness, and palpitations, proved annoying in several patients. These effects do not appear to present a contraindication to the use of 688-A.

It is suggested that therapy with 688-A be carried out on large groups of patients to determine whether its long-term effects on hypertensive patients will compare favorably with results of surgical treatment and whether this drug has a place in the therapy of essential hypertension.

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HISTOPATHOLOGY OF MUSCLE IN RHEUMATOID ARTHRITIS AND OTHER DISEASES

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AND
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THE MUSCLES, their coverings, and their attachments have been accorded slight but increasing attention in the pathology of the conditions known broadly as the rheumatic diseases. In 1843 Froriep, a pathologist in Weimar, noted fibrous flecks in muscles of patients with arthritis. He called these flecks rheumatic scars. Others denied their rheumatic origin or failed to find them.[1]

The English have long recognized painful soft tissues, juxta-articular and far from joints. This so-called fibrositis, characterized by pain and tenderness in ligaments, tendons, tendon sheaths, fascia, and muscles, has not been regarded as having any generally accepted histopathological features. Occasionally the term "myogelosis" has been used to describe the changes in tissues so affected. In 1904 Aschoff described infiltrated, degenerated areas in the myocardium of patients with rheumatic fever.[2] Geipel made similar discoveries about the same time.[3] What is now known as the Aschoff body was observed in many locations in the body with the exception of the joints.

Zenker called attention to foci of waxy degeneration of the skeletal muscles in rheumatic fever. The degenerative changes were later recognized as fibrinoid. This degeneration was followed by necrosis and resorption by large adventitial cells with round nuclei and by polymorphonuclear leucocytes. These changes were especially prominent in the muscles of the diaphragm, larynx, and tongue. The degeneration and the subsequent infiltrations were more frequent about the tendinous insertions. Scarring was the eventual outcome of these changes.

Recognition of the systemic character of rheumatoid arthritis has led to studies of tissues other than those of the joints themselves. Pain and tenderness in the soft tissues of the skeleton, distal from, as well as proximal to, the joint, always play a prominent role in the symptomatology of the disease. Indeed, the complaints or findings in the soft tissues may occasionally be the only manifestations of rheumatoid arthritis. In the presence of frank joint changes, the symptoms and findings in the muscle tend to be ascribed to the arthritis.

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1. Cited by Meyerburg, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, J. Springer, 1929, Vol. 9, part 1.

2. Aschoff, L.: Zur Myocarditisfrage, Verhandl. deutsch. path. Gesellsch. **2**:46, 1904.

3. Geipel, P.: Untersuchungen über rheumatische Myokarditis, Deutsches Arch. klin. Med. **85**:75, 1905.

Subcutaneous rheumatoid nodules are also extra-articular manifestations of changes in the soft tissue. The subcutaneous nodules are not necessarily even in the vicinity of joints. Painless rheumatoid nodules are sometimes found in patients without any other evidence of joint disease. They may be the only manifestation of the rheumatoid disease. The histology of rheumatoid nodules has been thoroughly described.

Since 1940 several investigators have described histological changes in the muscles of some patients with rheumatoid arthritis.

Curtis and Pollard [4] reported muscular atrophy, increased "interstitial nuclei," and perivascular infiltrations in biopsy specimens from the calf muscles of some of their patients with rheumatoid arthritis and also from those of five patients with Felty's syndrome, usually regarded as a variant of rheumatoid arthritis.

In 1942 and 1945 Freund and his co-workers [5] emphasized the occurrence of focal infiltrations in muscles of patients with rheumatoid arthritis. They emphasized the tendency of these infiltrations to be perineural.

Steiner, Freund, Leichtentritt, and Maun [6] called attention to the nodular character of the microscopic intramuscular lesions. The infiltrations were predominantly of round cells. Failing to find them in muscles of patients with other conditions, they called these nodular accumulations of cells typical of rheumatoid arthritis. Many have confirmed the finding of cellular infiltrations in the muscles of some patients with rheumatoid arthritis. Not all patients with rheumatoid arthritis show these infiltrations.[7] Clawson [8] and others [9] have reported observing similar nodules in the muscles of patients with rheumatic fever, lupus erythematosus, dermatomyositis, and scleroderma.

Steiner and Chason [10] also found focal cellular infiltrations in the latter diseases. According to them, these lesions can be differentiated from the muscular infiltrates of rheumatoid arthritis. They reported that these infiltrations occurred endomysially and perimysially but rarely epimysially in their patients with rheumatoid arthritis. They made little mention of perivascular infiltration in rheumatoid arthritis. Their muscle specimens were obtained by biopsy, during surgical operations, and at autopsy. The observation of similar soft-tissue changes in other diseases was taken to further relate these conditions, especially Felty's syndrome [4] and rheumatic fever,[8] to rheumatoid arthritis.

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4. Curtis, A. C., and Pollard, H. M.: Felty's Syndrome: Its Several Features Including Tissue Changes Compared with Other Forms of Rheumatoid Arthritis, Ann. Int. Med. **13**: 2265, 1940.

5. Freund, H. A.; Steiner, G.; Leichtentritt, B., and Price, A. E.: Peripheral Nerves in Chronic Atrophic Arthritis, Am. J. Path. **18**:865, 1942; abstracted, J. Lab. & Clin. Med. **27**: 1256, 1942; Nodular Polymyositis in Rheumatoid Arthritis, Science **101**:202, 1945.

6. Steiner, G.; Freund, H. A.; Leichtentritt, B., and Maun, M. E.: Lesions of Skeletal Muscles in Rheumatoid Arthritis: Nodular Polymyositis, Am. J. Path. **22**:103, 1946.

7. DeForest, G. K.; Bunting, H., and Kenney, W. E.: Rheumatoid Arthritis: Diagnostic Significance of Focal Cellular Accumulations in the Skeletal Muscles, Am. J. Med. **2**:40, 1947.

8. Clawson, B. J.; Noble, J. F., and Lufkin, N. H.: Nodular Inflammatory and Degenerative Lesions in Muscles from 450 Autopsies, Arch. Path. **43**:579 (June) 1947.

9. Gibson, H. J.; Kersley, G. D., and Desmarais, M. H. L.: Lesions in Muscle in Arthritis, Ann. Rheumat. Dis. **5**:131, 1946. Kersley, G. D.; Gibson, H. J., and Desmarais, M. H. L.: Nodule Formation in Rheumatic Disease, ibid. **5**:141, 1946.

10. Steiner, G., and Chason, J. L.: Differential Diagnosis of Rheumatoid Arthritis by Biopsy of Muscle, Am. J. Clin. Path. **18**:931, 1948.

The reported frequency of muscle changes in rheumatoid arthritis has varied among the authors (96%, Steiner and Chason [10]; 40%, Ogryzlo [11]). Most authors regard the focal accumulations of cells, the periarterial infiltration, and the interfibrillar collections of lymphocytes and plasma cells as nonspecific reactions. Almost all have seen these changes in those other conditions somewhat related to rheumatoid arthritis by similar collagen changes, such as disseminated lupus erythematosus, dermatomyositis, periarteritis nodosa, gout, Felty's syndrome, and Still's disease. Similar muscle changes have also been reported in diseases apparently unrelated to rheumatoid arthritis, such as myasthenia gravis, Addison's disease, and hyperthyroidism.[12]

The relation of the focal infiltrations to the blood vessels in rheumatic fever was emphasized by Chiari in 1938. He also described destruction in the vessels themselves. He and others called these changes specific for rheumatic fever, while noting the tendency of Coombs, Gräff, and Klinge to regard the infiltrates as nonspecific. Chiari differentiated these lesions in the skeletal tissue from the Aschoff nodule in the myocardium.

DeForest, Bunting, and Kenny reported the infiltrates in rheumatoid arthritis as being most commonly perivascular, not perineural. Kestler [13] also emphasized the vascular changes in rheumatoid arthritis. Several authors [14] have accorded arterial changes in rheumatoid arthritis some specificity, in spite of their finding arterial changes uncommonly in this disease. Such arterial inflammation in the skeletal muscles has been reported only rarely in rheumatic fever. Others [15] did not seem impressed by vessel changes in the muscles of patients with rheumatoid arthritis.

MATERIALS AND METHODS OF STUDY

We obtained sections from the gastrocnemius muscle of 16 patients with severe rheumatoid arthritis. The patients' ages varied from 41 to 80 years. Fourteen of the patients had had arthritis eight years or longer and were bedfast. One patient, the only Negro patient, had had symptoms for two years. Seven of the patients were men. Two of the patients had psoriasis. Three had marked amyloidosis and were the only patients with albuminuria. One other patient, poisoned with vitamin D, died while under observation. One man also had amyotrophic lateral sclerosis.

The activity of the rheumatoid process varied considerably. A few of the patients had no pain in an extremity at rest. The temperature of the skin over the joints was not elevated. All except one patient had sedimentation rates above 18 mm. per hour.

The muscles were slightly to moderately tender. Nodules could not be felt in these tender muscles.

We also studied biopsy specimens from the gastrocnemius of 10 patients with muscle wasting comparable with that present in the rheumatoid patients. This group included patients bedfast from Parkinsonism, hemiplegia, progressive muscular dystrophy, pulmonary tuberculosis, or cancer.

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11. Ogryzlo, M. A.: Chronic Inflammatory Lesions of Skeletal Muscle in Rheumatoid Arthritis and in Other Diseases, Arch. Path. **46**:301 (Oct.) 1948.

12. Steiner and Chason.[10] Ogryzlo.[11]

13. Kestler, O. C.: Histopathology of the Intrinsic Muscles of the Hand in Rheumatoid Arthritis, Ann. Rheumat. Dis. **8**:42, 1949.

14. Sokoloff, L.; Wilens, S. L., and Bunim, J. J.: Arteritis of Striated Muscle in Rheumatoid Arthritis, Am. J. Path. **27**:157, 1951.

15. Desmarais, M. H. L.; Gibson, J. J., and Kersley, G. D.: Muscle Histology in Rheumatic and Control Cases, Ann. Rheumat. Dis. **7**:132, 1948.

We included in our study one patient with disseminated lupus erythematosus without arthritis or joint complaints, one patient with dermatomyositis and severe rheumatoid arthritis, two patients bedridden for years with severe gouty arthritis, one patient with serum sickness, and one patient with acute rheumatic fever.

We also studied the muscles from the legs of rabbits inactivated for weeks or months in plaster cases.

The patients were in Cook County Hospital, the Cook County Hospital Arthritis Clinic, and Cook County Infirmary, Oak Forest, Ill. The sections were made in the Pathological Laboratory of the Presbyterian Hospital, Chicago.

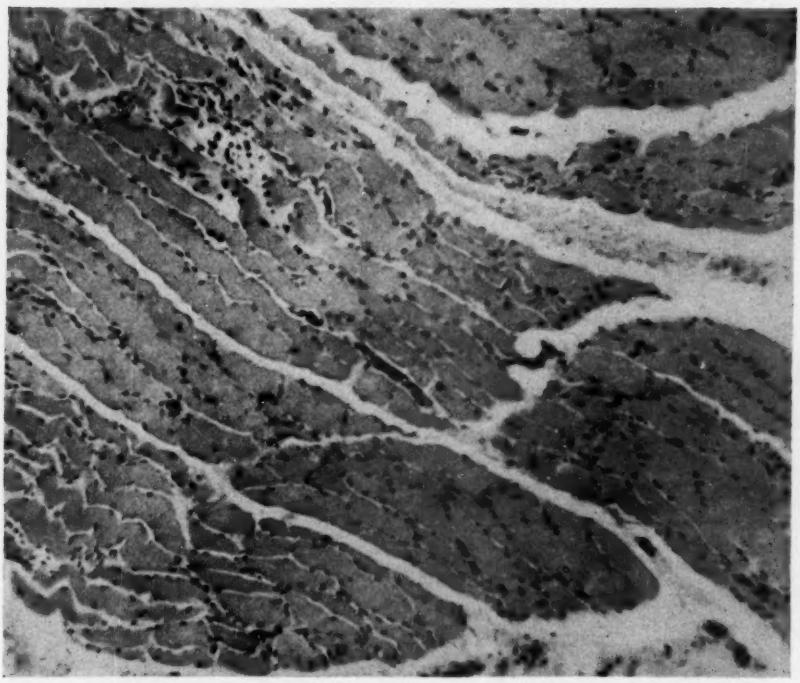

Fig. 1.—Biopsy section of gastrocnemius muscle of woman 41 years old, with rheumatoid arthritis for two years. Increase in sarcolemmal nuclei. Atrophy of fibrils. Round cells infiltrating focal areas of muscle degeneration.

The muscle sections were taken from the mid-calf, as far from the joints as possible. The biopsy specimens were approximately 2 cm. long, 1 cm. wide, and 1 cm. thick. A portion of each specimen was fixed in formalin and another portion in Zenker's solution. The sections were regularly stained with Mallory's aniline blue, with silver-lead chloride, and with Mallory's phosphotungstic acid stain. Six to 10 sections were cut at varying levels from each block.

RESULTS IN RHEUMATOID ARTHRITIS

From the rheumatoid patients, all sections showed muscular atrophy in some degree. In most of the specimens the muscle fibers and fibrils were narrow, roughly proportional to the gross muscular atrophy of the patient. Fat infiltration was common. The muscles frequently showed degeneration of various degrees. In

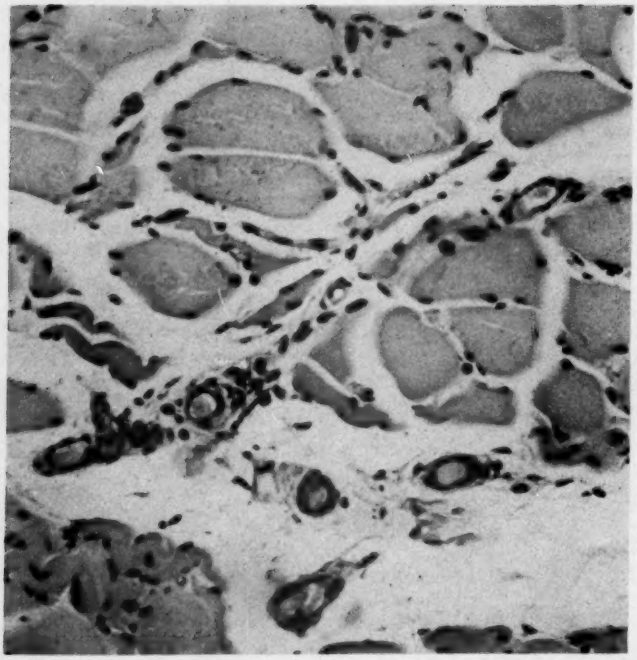

Fig. 2.—Biopsy section of gastrocnemius muscle of Negro woman 37 years old, with rheumatoid arthritis for four years. Increased sarcolemmal nuclei larger and rounder than normal. Pericapillary, infiltrating round cells.

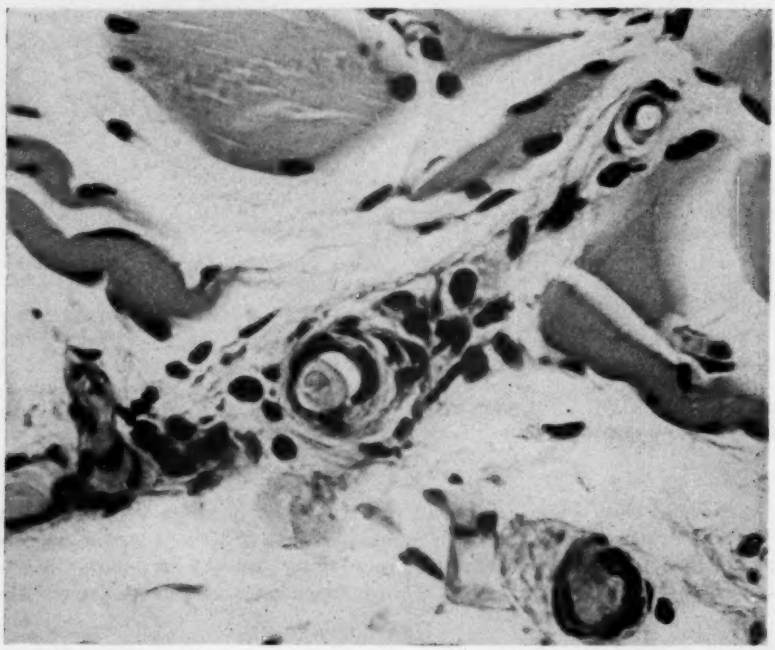

Fig. 3.—Section of Figure 2 under high-power magnification to show character of infiltrating cells (histiocytes, plasma cells, and epithelioid cells).

many instances the degeneration was focal. In some places only the muscle spindle remained. The degeneration was usually waxy, with loss of cross striation. It was impressive to see in some sections cross striation preserved even with far-advanced muscle deterioration. Necrosis was usually spotty. In very chronic cases scars were plentiful. There was not much evidence of proliferation of connective tissue. Where muscle parenchyma was missing, only fibrous tissue remained; the necrosis and scars were limited to areas not wider than two fibrils and about equally long.

The sections from all the rheumatoid patients showed an increase in the number of interfibrillar nuclei (Fig. 1). In proportion to the increase in number, the nuclei

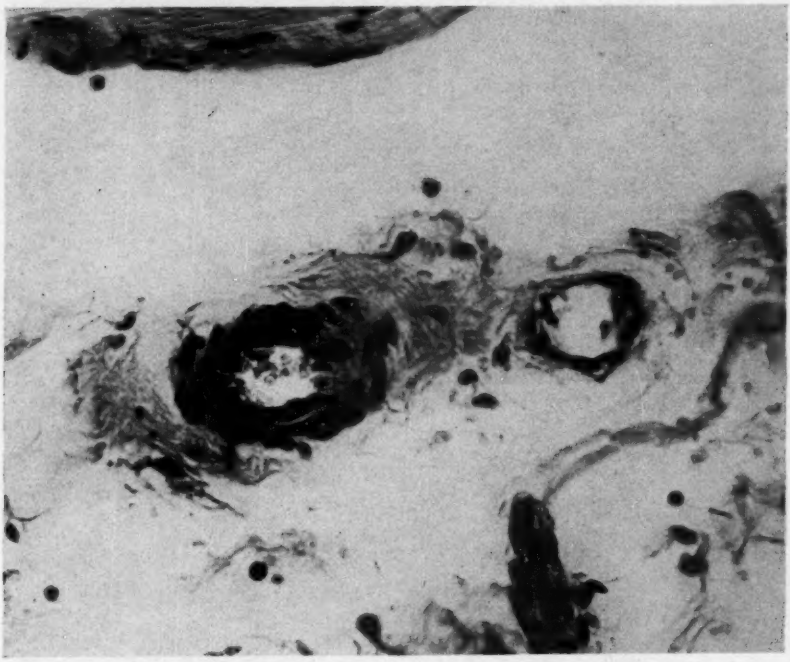

Fig. 4.—Muscle biopsy section from white woman 49 years old, with rheumatoid arthritis for nine years and vitamin D poisoning. Periarterial infiltration in surrounding connective tissue.

were larger, rounder, and paler than the elongated, thin, heavily stained sarcolemmal nuclei of normal muscle. These large pale nuclei were especially numerous in the spots of muscular degeneration.

These nuclei were actually increased in number and not merely apparently more numerous because of the atrophy of the intervening fibrils. They were quite different from the normal nuclei. Occasionally they were grouped to form giant cells of the Sternberg type. They have been considered sometimes as myophages and at other times as signs of preparation for regeneration. Certainly some of the nuclei belonged to infiltrating histiocytes. The accumulations of the large pale nuclei and

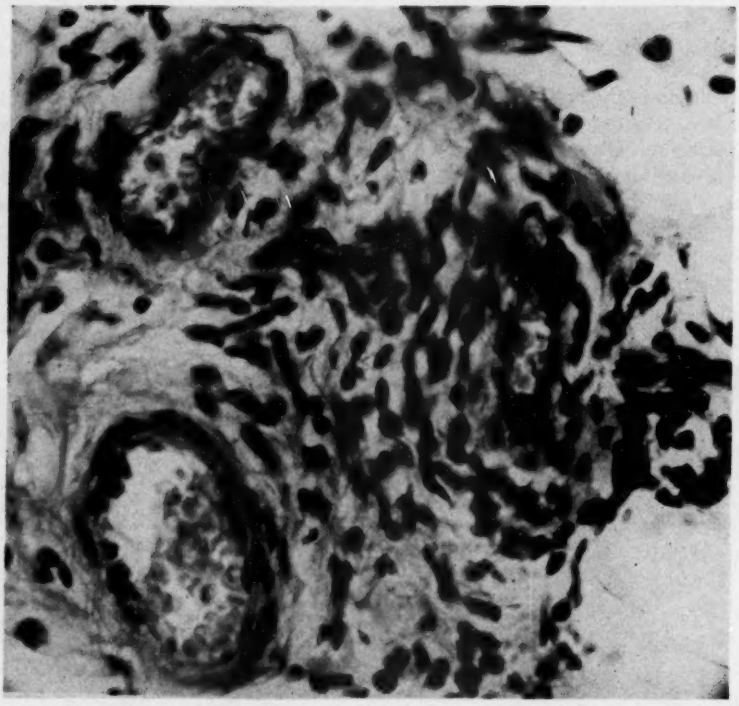

Fig. 5.—Rheumatoid arthritis with dermatomyositis in a man 74 years old. Rheumatoid arthritis was present 20 years and dermatomyositis six months. Section taken from fat of intermuscular septum. Small venule. Capillary with marked small pericapillary infiltration.

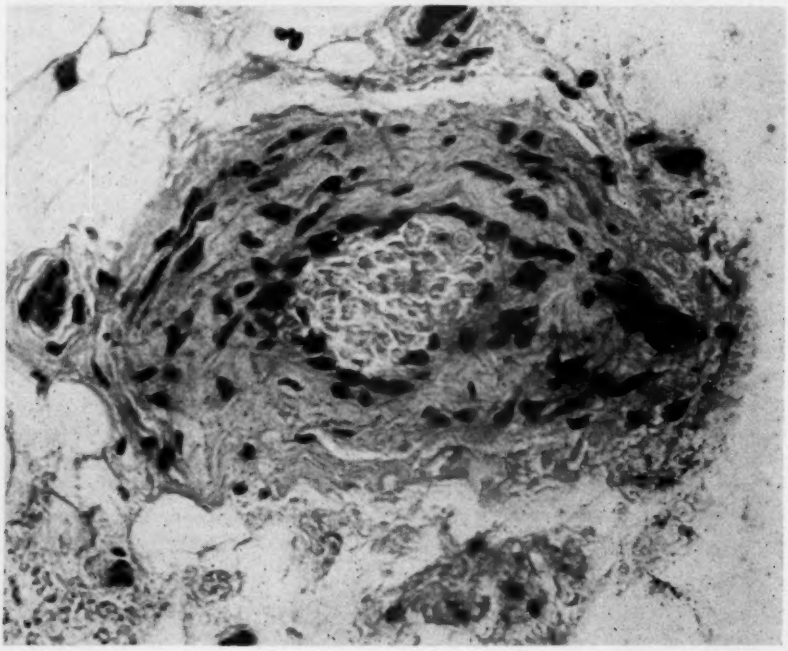

Fig. 6.—Biopsy section of gastrocnemius muscle from white man 38 years of age, with rheumatoid arthritis for eight years. Infiltration into wall of arteriole. Histiocytes and epithelioid cells.

the occasional giant cells (myoclasts) were always in areas of marked muscle degeneration or necrosis. Frequently these foci also contained lymphocytes, less usually plasma cells, and still more rarely neutrophiles.

More characteristic of the histopathological changes of the muscle in rheumatoid arthritis were the perivascular infiltrations. These were observed around the smallest arterioles and capillaries. The very smallest arteries were usually affected (Figs. 2 to 5, and 9). One biopsy specimen showed infiltration of the wall of an arteriole (Fig. 6). Arterial infiltration was slight in all sections except those from

Fig. 7.—Biopsy section of gastrocnemius muscle from man 77 years old, with "burned-out" rheumatoid arthritis of 17 years' duration. Atrophy and degeneration of muscle fibrils; replacement of muscle by fat. General increase in perimysial nuclei. Giant cells (myoblasts).

the patient with dermatomyositis. The walls of the small infiltrated vessels in rheumatoid arthritis seemed not to be destroyed. They were not obstructed by proliferation of the intima or by thrombosis.

Perivascular infiltration was present in all the patients with rheumatoid arthritis except a man 77 years of age who had had rheumatoid arthritis for 17 years. No signs of active joint disease were detectable in this bedridden man; the arthritic process could be characterized as "burned-out." Scars were numerous in the sections from this man's muscle (Fig. 7). His sections showed no periarteritis.

Peripheral nerves were occasionally recognized. Perineural infiltration was not seen in any of the sections.

A biopsy specimen from a woman with rheumatoid arthritis was studied before two weeks of intensive cortisone (cortone®) administration. Although the patient's circulating eosinophiles fell from 180 to 0 coincidentally with a dramatic improve-

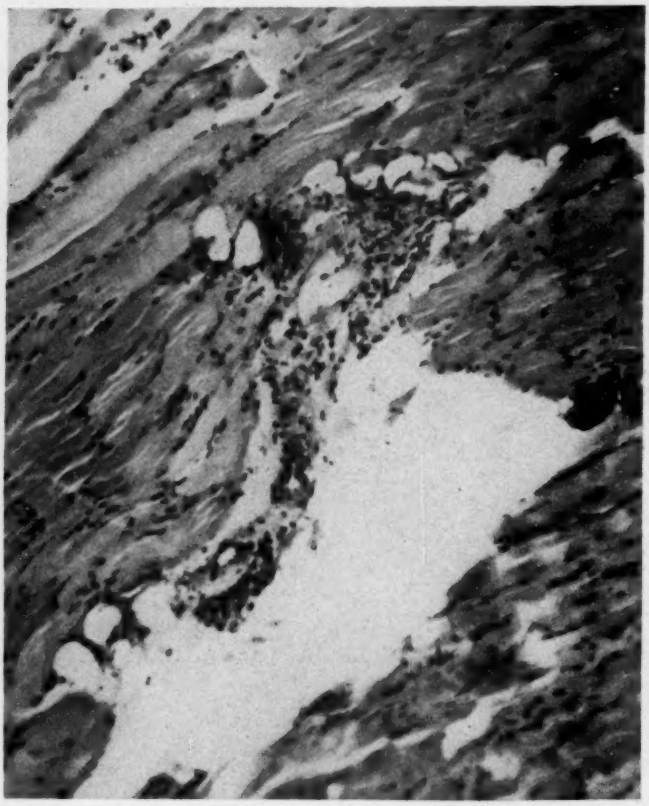

Fig. 8.—Biopsy section of gastrocnemius muscle of woman 42 years old, with hemiplegia for five years. Section is from muscle on paralyzed side. Increase in interfibrillar nuclei and replacement of muscle by fat. Focal accumulation of cells.

ment in her clinical condition, the muscle lesion was unchanged or even more marked after and during treatment.

The severity of muscle changes did not bear any relation to the speed of erythrocyte sedimentation.

The focal infiltrations and perivascular inflammation observed in rheumatoid muscles were not seen in Strümpell-Marie disease (rheumatoid arthritis of the spine), unless the latter was complicated by peripheral rheumatoid arthritis.

RESULTS IN CONDITIONS OTHER THAN RHEUMATOID ARTHRITIS

The muscular atrophy and increase in perimysial nuclei were also seen in the paretic extremities of the patients with hemiplegia (Fig. 8), in the wasted extremities of the patients with Parkinsonism, and to a much less degree in the atrophic muscles of the immobilized legs of rabbits. The focal accumulations could be found, though less commonly, even in the wasted muscles of patients without arthritis. The atrophy and increase in interfibrillar nuclei were also seen in the wasted muscles of the patient with disseminated lupus erythematosus.

As would be expected, the changes in the muscles from the patient with dermatomyositis were striking. However, they differed quantitatively rather than in

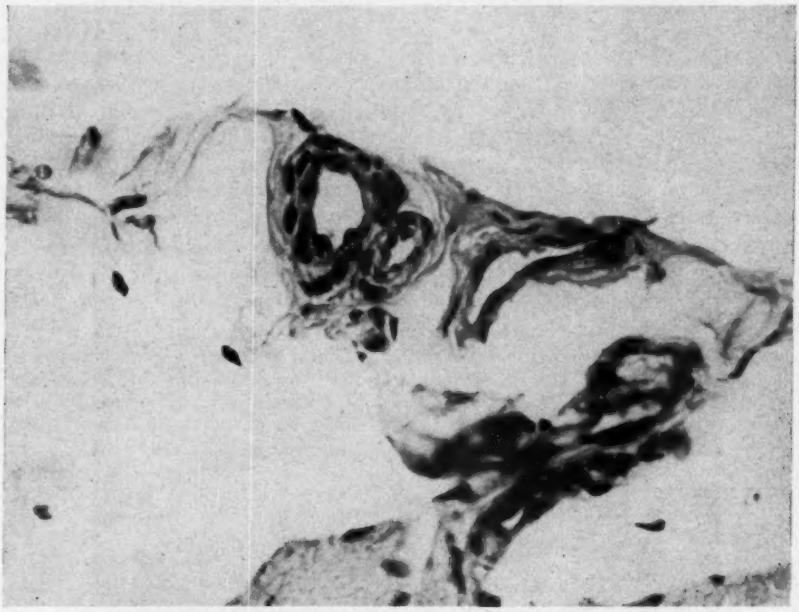

Fig. 9.—Section of Figure 1 under high-power magnification to show perivascular capillary infiltration in connective tissue.

kind of reaction from muscles in rheumatoid arthritis (Fig. 9). The waxy degeneration was more extensive. The infiltration between the fibrils was more marked and, as emphasized by Steiner and Chason, tended to have an endomysial and perimysial rather than an epimysial distribution. We could easily see foci within the muscle exactly as in the muscles of rheumatoid arthritis, possibly because of the antecedent and then coexistent rheumatoid arthritis. The foci were larger than those in the muscles of patients with uncomplicated rheumatoid disease. They were the only focal reactions containing eosinophiles. The periarteritis was also severe in the section from the dermatomyositis patient.

The only changes in the muscle of the patient with the severe reaction to tetanus antitoxin were a mild increase in the perimysial cells and a few focal accumulations between fibrils (Fig. 10).

There were no histopathological changes in the muscle from the patient with acute rheumatic fever.

The Negro woman with disseminated lupus erythematosus was very emaciated. Microscopically the muscles appeared swollen rather than atrophic. There were foci of degeneration to the point of cyst formation. Focal areas of destroyed muscle were surrounded with round cells.

Fig. 10.—Biopsy section of gastrocnemius muscle from woman 32 years old on third day of serum reaction (tetanus antitoxin) and severe urticaria. Increase in perimysial nuclei. Edema of fibrils.

The sections from one of the men with chronic gouty arthritis showed only atrophic muscle and marked arteriolosclerosis. The muscle from the other man with chronic gouty arthritis showed more marked atrophy, more interfibrillar nuclei, and also frequent, scattered areas of severe muscle degeneration. Neither of the sections of muscle from the gout patients showed perivascular infiltration.

COMMENT

Apparently the most prominent histopathological features in muscles of patients with rheumatoid arthritis are atrophy and increase in the number, size, and shape of perimysial nuclei. These findings are common to all patients with disuse atrophy.

Common in rheumatoid arthritis, but also not uncommon in disuse atrophy, are interfibrillar collections of round cells.

The muscle damage was severer in the preparations from rheumatoid arthritis than in the sections from paralyzed extremities. Degeneration, necrosis, and scarring, commonly present in the muscles in rheumatoid arthritis, were not encountered in immobilized muscles.

Mild perivascular infiltration was seen in muscles from all patients with rheumatoid arthritis except one. It was not encountered in patients without arthritis, in those with gouty arthritis, or in the patient with the arthritis of serum sickness.

Perivascular infiltration was the only unusual finding peculiar to rheumatoid arthritis in muscles of the many conditions studied.

SUMMARY

Atrophy and degeneration of muscle in rheumatoid arthritis were similar to that seen in other inactive muscles. The degeneration of muscle with necrosis and scarring was encountered only in inflammatory conditions, such as rheumatoid arthritis, dermatomyositis, and disseminated lupus erythematosus.

Increase in number and change of type of perimysial nuclei were found regularly to accompany atrophy.

Interfibrillar focal infiltrations of mononuclear cells were present in all the biopsy specimens, including those from paretic muscles.

Mild perivascular infiltration was observed in 15 of the 16 patients with rheumatoid arthritis. The infiltration was slight and occurred only about the smallest vessels.

Helpful suggestions in this study were made by Dr. George Hass, Pathologist in the Presbyterian Hospital of Chicago, Dr. Granville Bennett, Professor of Pathology in the University of Illinois College of Medicine, and Dr. John Kiselis, Pathologist in the West Suburban Hospital, Oak Park, Ill.

TREATMENT OF PNEUMOCOCCAL MENINGITIS WITH LARGE DOSES OF PENICILLIN

A Series of Twenty Consecutive Cases

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THE RATIONALE for employing large doses of parenterally administered penicillin as a standard method of therapy for pneumococcal meningitis was first stated by Dowling and his group in 1949.[1] Their observations on a small series of 21 cases indicated that 1,000,000 units of aqueous crystalline penicillin administered intramuscularly every two hours was superior to all other previously described regimens of therapy for the disease.[2] It was their opinion that the use of intrathecally administered penicillin and/or the combination of a sulfonamide with penicillin was unnecessary, although in patients in coma on admission a single initial intrathecal dose of penicillin may be given. Dowling's recommended program for the therapy of pneumococcal meningitis has been followed in a small series of patients treated in this institution, and the results lend further proof to his original contention.

METHODS

The hospital courses of 20 consecutive patients[2a] with bacteriologically proved pneumococcal meningitis have been reviewed in detail. The patients were hospitalized in the medical or pediatric wards of the Syracuse Medical Center Hospitals (University, Memorial, City, and Crouse-Irving Hospitals) and were treated in a more or less uniform fashion between April, 1949, and August, 1951. Clinical and laboratory details were recorded in similar manner and in a single place. Pneumococci were recovered from spinal fluid or blood or both in every patient. Isolation and typing of all organisms were performed by Miss Winifred Osborne, Department of Bacteriology. In certain cases no more than identification of the pneumococcal pool was possible because of the lack of certain types of specific antisera.

Blood and spinal fluid concentrations of penicillin were measured in a few instances by the cup-plate assay method, using Sarcina lutea as the test organism.[3]

Dosage schedules of penicillin prescribed for all patients followed Dowling's recommendations. Seven adults, three teen-age, and two small children initially received 1,000,000 units of

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This study was supported by a grant from Bristol Laboratories, Inc., Syracuse, N. Y.

From Department of Medicine, State University of New York at Syracuse College of Medicine.

1. (*a*) Dowling, H. F.; Sweet, L. K.; Robinson, J. A.; Zellers, W. W., and Hirsch, H. L.: Treatment of Pneumococcic Meningitis with Massive Doses of Systemic Penicillin, Am. J. M. Sc. **217**:149 (Feb.) 1949. (*b*) Dowling, H. F.; Hirsch, H. L.; Sweet, L. K.; Zellers, W. W., and Robinson, J. A.: Treatment of Pneumococcic Meningitis with Massive Doses of Penicillin Systemically, Proc. Am. Federation Clin. Res. **5**:2, 1949.

2. Ruegsegger, J. M.: Pneumococcal Meningitis, Ann. Int. Med. **17**:693 (Oct.) 1942.

2a. One person is counted as a patient twice since he was treated for pneumococcal meningitis on two different occasions.

3. Cup Plate Assay of Penicillin Concentrations in Plasma, in Methods in Medical Research, edited by V. R. Potter, Chicago, The Year Book Publishers, Inc., 1948, Sec. 1, p. 25.

crystalline penicillin in aqueous solution every two hours intramuscularly. In three other small children, the initial and priming doses of penicillin were reduced to 500,000 units (Table 1). The remaining five adult patients were given lesser amounts of penicillin for 3 to 13 days and were included in the series because massive therapy became necessary before remission of the meningitis was accomplished. Adjuvant therapy was continued in five patients for at least a week. A single intrathecal dose of penicillin was given to two patients, and a third patient received five injections. He was included because combined therapy proved unsuccessful. The therapeutic regimen of massive therapy was extended until clinical remission seemed complete; no specific limit was, or is, advocated.

RESULTS

Clinical and laboratory data on 20 patients with pneumococcal meningitis are presented in Table 1, and a summary of the results is outlined in Table 2. Fifteen of the 20 patients recovered; 5 died.

The Dead.—Five patients died during the period of observation (Cases 1, 2, 3, 4, and 5, Table 1). Three of these, aged 2 months, 15 years, and 62 years, died within the first 24 hours of hospitalization, and none received more than 12 doses of penicillin. Clinical improvement did not occur. Each had bacteremia upon admission; each had had the meningeal complication for at least 24 hours before admission; the adult was an alcoholic and had associated cardiac disease prior to the infection, and the teen-age boy had received a moderately severe head injury with a bowling pin.

Two patients, aged 82 and 83 years, died after receiving therapy for 12 and 15 days, respectively. In both, evidences of meningeal infection had subsided and the cause of death was not considered to be an infection in either. In one patient (Fig. 1) heart failure and uremia developed, and he died of a massive pulmonary embolus. The panophthalmitis present on admission had subsided, although the eye was totally destroyed and enucleation was inevitable. His spinal fluid and blood cultures were sterile before death, and he was afebrile. Autopsy was not performed. The other patient died on the 13th hospital day of pneumonia that had not resolved. At autopsy there was no evidence of meningitis.

The Living.—Fifteen patients survived and were cured of all evidences of meningitis. Central nervous system residua occurred in only two patients. The seventh-nerve palsy in one was not of major importance and did not preclude a complete return to active life. In this single instance the onset of the complication could not be dated. Its presence was first realized on the fourth day of treatment; the patient was severely ill on admission, and it is likely that the lesion existed at the time therapy was first instituted. The vestibular and hearing defect in the second patient gradually cleared, and after six months there was no significant loss of either function.

There was no instance of relapse after adequate therapy. One patient appeared twice in the series (Table 1, Cases 19 and 20). His first pneumococcal (Pool IV) meningitis was completely cleared in 17 days in April, 1949. Almost exactly one year later he acquired the disease again, with Type 3 Diplococcus pneumoniae as the causative agent. He again recovered completely and had no central nervous system residua when last seen 18 months after the second bout. During the first episode, blood cultures were sterile and pneumococci were cultured from spinal fluid and material from his sinuses. With the second, the patient was bacteremic. Both attacks of meningitis originated with a badly infected, chronic maxillary sinusitis. During the year after his first infection and for the 18 months of obser-

TABLE 1.—*Summary of Twenty Cases of Pneumococcal Meningitis Treated with Large Intramuscular Doses of Penicillin* *

Case No.	Sex and Age	Associated Condition	Diplococcus pneumoniae Pool or Type		Duration in Days		Treatment with Penicillin	Accessory Treatment	Duration of Therapy Before Temperature Below 100 F., Days	Result	Comment
			Blood	Spinal Fluid	Before Therapy	Penicillin Therapy					
1	2 mo. F	.....	....	Type 7	1	1	500,000 U. q. 2h. I. M. and I. V.	....	..	Died in 24 hr.	No response; in shock
2	62 yr.; M	URI and right upper lobe pneumonia	+	+	3	1	1,000,000 U. q. 2h. I. M.	....	..	Died in 24 hr.	No response; in shock; chronic alcoholism in past
			Not identified								
3	15 yr.; M	Head injury; URI	Type 1	Type 1	1	1	1,000,000 U. q. 2h. I. M. or I. V. (6 doses)	....	1	Died	Fulminating course unabated by therapy
4	82 yr.; M	Lobar pneumonia	Type 1	....	10	4	1,000,000 U. q. 2h. I. M.	....	..	Died in 12 days	Postmortem examination: healed meningitis
						8	1,000,000 U. q. 2h. I. M.				
5	83 yr.; M	Panophthalmitis for 3 wk.; associated sinusitis	Type 15 Eye	Type 15	1	15	1,000,000 U. q. 2h. I. M.	....	..	Died in 15 days	See Fig. 1; died in uremia and cardiac decompensation with massive pulmonary embolism
			Nose Throat	Type 15							
6	4 mo.; F	URI and OMPA	....	Type 14	1	10	500,000 U. q. 2h. I. M.	Sulfadiazine for 13 days	6	Cured; no residua	Prompt response; sulfadiazine given later as conservative measure
7	2 mo.; M	Diarrhea for 1 wk.	....	Type 7	1	7	500,000 U. q. 2h. I. V.	Sulfadiazine for 14 days	2	Cured; no residua	Sulfadiazine only for urinary tract infection
						7	100,000 U. q. 2h. I. V.				
8	2½ yr.; M	Coryza; pharyngitis	....	Type 18	3	3	1,000,000 U. q. 3h. I. V.	....	7	Cured; residua diminishing	Bilateral deafness and vestibular defect during convalescence
						15	500,000 U. q. 2h. I. M.				
						11	250,000 U. q. 6h. I. M.				
9	5 mo.; M	URI and cough for 1 wk.	....	Type 15	1	3	1,000,000 U. q. 2h. I. M.	Single dose each:	8	Cured; transient palsies cleared	Residual spinal fluid pleocytosis persisted; initial convulsion, transient palsies
						7	500,000 U. q. 2h. I. M.	10,000 U. penicillin I. T.			
						8	400,000 U. b. i. d. I. M.	and 2.5 gm. sulfadiazine I. V.			
10	10 yr.; M	URI 1 wk. and pharyngitis	Type 11	....	1	6	400,000 U. q. 2h. I. M.	3 gm. sulfadiazine q. d. for 7 days	3	Cured; no residua	Negative spinal fluid in 7 days before sulfadiazine
						1	1,000,000 U. q. 2h. I. M.				

11	11 yr.; F	Coryza and cough for 1 wk.	....	+ (Not identified)	4	6 4 3	1,000,000 U. q. 2h. I. M. 500,000 U. q. 3h. I. M. 400,000 U. b. i. d. I. M.	4 gm. sulfadiazine q. d. for 13 days	8	Cured; no residua	Prompt response
12	32 yr.; M	URI for 1 wk.	....	Type 11	1	8 12	800,000 U. q. 2h. I. M. 1,000,000 U. q. 2h. I. M.	....	8	Cured; no residua	Inadequately treated pneumococcal meningitis 1 yr. before; subsequent severe headaches, worse before P. I
13	43 yr.; F	Recurrent severe ethmoiditis	Type 10a	Type 10a	2	14	1,000,000 U. q. 2h. I. M.	3 gm. aureomycin q. d. for 7 days	4	Cured; no residua	High spinal fluid protein after 6 mo.
14	57 yr.; F	URI 2½ wk.; OMPA (left) 4 days; on admission left lower lobe pneumonia	....	Pool 2 Type 7	3	22 2	1,000,000 U. q. 2-4h. I. M. 200,000 U. q. 4h. I. M.	....	11	Cured; no residua	Partial palsies right cranial 3d and 7th nerves cleared; 1 wk. had hematuria, cause undetermined
15	60 yr.; F	OMPA (left) and acute arthritis on admission	Pool 3	Pool 3	1½	6 13	50,000-200,000 U. q. 3h. I. M. 1,000,000 U. q. 2h. I. M.	6 gm. sulfadiazine for 7 days and 1 dose 10,000 U. penicillin I. T.	5	Cured; no residua	Arteriosclerotic heart disease with decompensation complicated therapy; poor response 1st 6 days
16	55 yr.; M	Right upper lobe pneumonia on admission	Pool 1	....	4	8 1 9	1,000,000 U. q. 2h. I. M. 300,000 U. q. 4h. I. M. 300,000 U. b. i. d. I. M.	3 gm. streptomycin q. d. × 8; 2 gm. streptomycin q. d. × 7	5	Cured; no residua	Pneumonia complicated treatment; streptomycin later for urinary infection
17	68 yr.; M	Recurrent sinusitis; eye abscess	Type 7	Type 7	5	9 3 28	1,000,000 U. q. 2h. I. M. 300,000 U. q. 3h. I. M. 600,000-800,000 U. q. d. I. M.	....	21	Cured; preceding hemiparesis persisted	Vitreous body abscess right eye + (?) cerebral thrombophlebitis
18	65 yr.; F	Sore throat 1 wk.; OMPA 5 days; pneumonia	Type 5	Type 5	1	9	1,000,000 U. q. 2h. I. M.	....	5	Cured; no residua	Meningitis developed during penicillin therapy of 300,000 U. q. d. for pneumonia
19	30 yr.; M	OMPA 3 days (recurrent)	....	Pool 4	1	13 4	100,000 U. q. 3h. I. M. × 13 days 1,000,000 U. q. 2h. I. M.	12 gm. sulfadiazine q. d. for 11 days; also 5 doses 10,000 U. penicillin I. T.	5	Cured; no residua; first patient in series	Improved but not cured 2 wk.; therapy increased; pleocytosis persistent in CSF with penicillin I. T.
20	31 yr.; M	OMPA (left) 4 days; mastoiditis left	Type 3	Type 3	1	11	1,000,000 U. q. 2h. I. M.	5 gm. sulfadiazine I. V. q. d. for 5 days	5	Cured; left facial palsy	Same patient as above; roentgen evidence of mastoiditis

* I. M. means intramuscularly; I. V., intravenously; I. T., intrathecally; URI, upper respiratory infection; OMPA, otitis media purulenta acuta; P. I., present injection.

TABLE 2.—*Summary of Treatment and Results in Twenty Cases of Pneumococcal Meningitis Treated with High Doses of Penicillin Intramuscularly* *

	No. of Cases	No. Survived
1. Treated with penicillin alone. Two patients died subsequent to clinical and laboratory cure; one died of pulmonary embolism; the other in coma with unresolved pneumonia	7	5
2. Treated with sulfonamide adjuvant	8	8
3. Treated with streptomycin adjuvant	1	1
4. Treated with aureomycin adjuvant	1	1
5. Treated with penicillin alone but with death intervening in first 24 hr. of therapy	3	..
Total	20	15

* Eleven of the 20 patients were in coma at start of treatment; 7 survived.

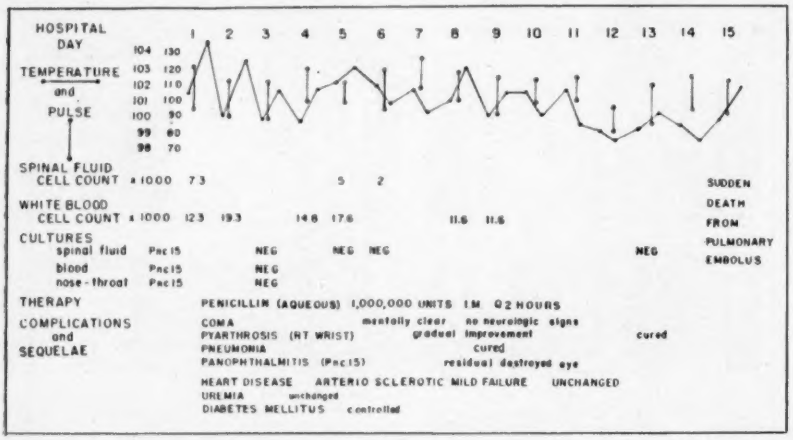

Fig. 1.—Course of pneumococcal meningitis treated with massive doses of penicillin in Patient 5, a white man aged 83. *Pnc* means Pneumococcus.

vation after the second, the patient has had clear spinal fluid rhinorrhea. Therapy during the first episode was initially prescribed to conform with the then popular program, i. e., 100,000 units of aqueous penicillin intramuscularly every three hours, with the addition of 10,000 units of penicillin by the intraspinal route every other day for five doses. Sulfadiazine was also administered in massive amounts (12 gm. daily), and the combined program was continued for 13 days. The patient's condition improved during this period, but he continued to have low-grade fever, and his spinal fluid remained markedly abnormal with pleocytosis and elevated protein and reduced sugar contents. Cultures of spinal fluid and material from the nose and throat became sterile. Because of the poor response, therapy was shifted to the massive dose regimen. Defervescence promptly occurred; toxicity lessened within 48 hours, and in 96 hours the patient was clinically well. The abnormal spinal fluid findings reverted gradually to normal over a three-week period. Massive dose therapy was started immediately on the day of recurrence of infection one year later, and the response was satisfactory.

Two other patients received single intrathecal doses of 6,000 and 10,000 units early in the treatment period. Both patients were acutely ill. The course of neither infection was appreciably altered by the intrathecal dose.

Ten of the 20 patients received other drug therapy; 8 were given sulfadiazine. One patient received aureomycin (Fig. 2), and one patient received streptomycin. It was not possible to evaluate the clinical efficacy of combined versus single drug regimens in this series (Table 2). It was certainly apparent that those receiving a second antimicrobial agent did not respond in a fashion significantly different from those receiving large doses of penicillin alone. Figure 2 shows the clinical course of a patient receiving combined therapy.

The clinical course of the 15 survivors was gratifying. The temperature returned to normal in an average of 6.5 days; coma cleared within two days in five of the seven so affected and within four days in the other two. Other clinical evidences of meningitis subsided promptly, and after seven days in all 15 it was evident that a complete remission had been accomplished. The disappearance of pleocytosis

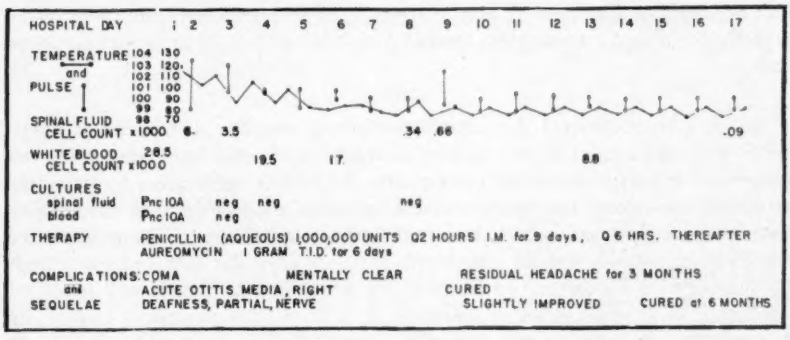

Fig. 2.—Course of pneumococcal meningitis treated with massive doses of penicillin and with some aureomycin in Patient 13, a white woman, aged 43. *Pnc* means Pneumococcus.

TABLE 3.—*Comparison of Clinical Data in This Series of Twenty Cases with Those in Dowling's Series of Twenty-One Cases*

	No. of Patients	Age, Yr.		Duration of Illness Prior to Therapy		Presumed Source of Spread of Pneumococci			Survivors		Adjunctive Therapy
		Under 1	Over 40	Patients	Days	Site	No.	No. Died	No. Days' Treatment	No. Patients	
Dowling [1]	21	3	14	12 (known)	Average, 5; range, 1-18	Lung	5	2	5-9	5	Sulfonamide, 13
						Ear	2	0	10-13	5	
						Heart	2	2	14-17	3	Penicillin
						Head injury	1	0			intrathecally, 4
						Unknown	11	4			
Present study	19	4	9	18	Average, 2.5; range, 1-4	Lung	3	2	5-9	2	Sulfonamide, 8
						Ear	2	0	10-13	3	
						Lung and ear	2	0	14-19	6	Penicillin
						Heart	0	0	Over 20	3	intrathecally, 2
						Head injury	1	1			
						Sinus	1	0			
						Sinus and eye	2	1			
						Sinus and ear	1	0			
						Upper respiratory infection	5	0			
						Unknown	2	1			

could not be evaluated by time, although in the majority of those examined lumbar punctures on the seventh or eighth day of treatment revealed spinal fluid cell counts below 10. Spinal fluid was sterilized of pneumococci within 24 hours in 16 of the 17 patients who survived more than one day and within 48 hours in the other. Figure 2 shows the course of the infection in a patient who responded in standard fashion.

Table 3 compares certain observations on the disease and its therapy in this series with those of Dowling. Twelve surviving patients in this series received therapy for 6 to 19 days; none of Dowling's 13 survivors were treated for longer than 17 days. Therapy was extended for 24 to 40 days in three other patients in the present group because of the persistence of chronic middle ear infection and abscess of the eye (Case 17, Table 1), the appearance of a new urinary tract infection (Case 14, Table 1), and the development of nerve-deafness and vestibular defect (Case 8, Table 1). In no instance in this series was therapy for evidences of meningitis indicated after the 20th day.

During the period of acute meningitis, spinal fluid concentrations of 0.05 to 0.5 unit per cubic centimeter were obtained with 1,000,000 units penicillin given intramuscularly. Blood concentration reached peak levels of 5 to 20 units with the same dosage.

COMMENT

It must be emphasized that massive parenteral penicillin therapy for pneumococcic meningitis is advocated because it appears to be the best therapy for the disease. Early experience with the regimen of 1,000,000 units given by the intramuscular route every two hours has resulted in an appreciable drop in mortality rate from the infection in both Dowling's and our experience. The incidence of complicating sequelae and the total length of illness have also been reduced. With consideration of the latter two features, the added cost of the therapy needs no apology. In a small series of 20 cases, it is impossible to predict statistically the reduction in mortality rate from the accepted 49% as reported by Dowling,[1a] but there can be no doubt that the regimen warrants priority usage until better figures are obtained with some other program.

For the reason cited by Dowling,[1a] the use of intrathecally administered penicillin is not desirable (poor penetration to all areas of infection and its irritative qualities), and it is quite possible that even the first dose is unnecessary in comatose patients. As the use of adjuvant drugs does not apparently add to the efficacy of penicillin therapy, as seen in both this and Dowling's series, aureomycin and/or sulfadiazine need not be employed. On the other hand, their concomitant administration is not necessarily contraindicated, for there is no evidence that either interferes with the action of penicillin against pneumococci.

SUMMARY

A small series of 20 patients with bacteriologically proved pneumococcic meningitis were treated with large doses of parenterally administered penicillin. The recommended dose is 1,000,000 units every two hours for at least one week, or until clinical remission seems secure. Adjuvant therapy with sulfonamides or aureomycin apparently adds nothing to efficacy of the regimen, and intrathecal administration of penicillin is probably contraindicated.

CONDITION OF THE HEART FOLLOWING BERIBERI AND MALNUTRITION

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BERIBERI is recognized as an infrequent but a definite cause of heart failure. Although beriberi heart disease can be severe and frequently fatal in its acute stage, there is very little in the medical literature on the end-result of this type of heart disease, nor has it been shown whether persons who recover from beriberi may have a chronic form of beriberi heart disease.

This report is on a study of the cardiac condition of 109 men who survived the acute effects of beriberi and severe malnutrition suffered during 44 months in Japanese prisons during World War II.

HISTORY

The medical literature on beriberi heart disease contains reports on (1) the Oriental form, occurring where the diet consists chiefly of rice and is inadequate in general,[1] (2) the Occidental form, most commonly seen in chronic alcoholism and occasionally in a variety of conditions [2] in which there is a deficiency in food

1. (*a*) Keefer, C. S.: The Beriberi Heart, Arch. Int. Med. **45**:1 (Jan.) 1930. (*b*) Scott, L. C., and Herrmann, G. R.: Beriberi ("Maladie des Jambes") in Louisiana, with Especial Reference to Cardiac Manifestations, J. A. M. A. **90**:2083 (June 30) 1928. (*c*) Morgan H. J.; Wright, I. S., and van Ravenswaay, A.: Health of Repatriated Prisoners of War from the Far East, ibid. **130**:995 (April 13) 1946.

2. (*a*) Weiss, S., and Wilkins, R. W.: The Nature of the Cardiovascular Disturbances in Nutritional Deficiency States (Beriberi), Ann. Int. Med. **11**:104 (July) 1937. (*b*) Weiss, S.: Occidental Beriberi with Cardiovascular Manifestations: Its Relation to Thiamin Deficiency, J. A. M. A. **115**:832 (Sept. 7) 1940. (*c*) Goodhart, R., and Jolliffe, N.: The Role of Nutritional Deficiencies in the Production of Cardiovascular Disturbances in the Alcohol Addict, Am. Heart J. **15**:569 (May) 1938. (*d*) Blankenhorn, M. A.: Diagnosis of Beriberi Heart, Ann. Int. Med. **23**:398 (Sept.) 1945. (*e*) Blankenhorn, M. A.; Vilter, C. F.; Scheinker, I. M., and Austin, R. S.: Occidental Beriberi Heart Disease, J. A. M. A. **131**:717 (June 29) 1946. (*f*) Gelfand, D., and Bellet, S.: Symposium on Nutritional Disorders: Cardiovascular Manifestations of Beriberi Based on Study of 10 Patients, M. Clin. North America **33**:1643 (Nov.) 1949. (*g*) Dustin, C. C.; Weyler, H., and Roberts, C. P.: Electrocardiographic Changes in Vitamin B_1 Deficiency, New England J. Med. **220**:15 (Jan. 5) 1939. (*h*) Campbell, S. B. B., and Allison, R. S.: Pellagra, Polyneuritis, and Beriberi Heart, Lancet **1**:738 (April 20) 1940. (*i*) Toreson, W. E.: Diffuse Isolated Myocarditis Associated with Dietary Deficiency, Arch. Int. Med. **73**:375 (May) 1944. (*j*) Paulley, J. W., and Aitken, G. J.: Case: Cardiovascular Beriberi, Lancet **2**:440 (Sept. 30) 1944. (*k*) Beriberi Heart, Symposium Section, Internat. M. Digest **48**:370 (June) 1946. (*l*) Epstein, S.: Observations on Beriberi Heart Disease, Am. Heart J. **34**:432 (Sept.) 1947. (*m*) Modern, F. W. S.; Leik, D. W., and Rapaport, S.: Nutritional Heart Disease, Am. Pract. & Digest Treat. **1**:1044 (Oct.) 1950. (*n*) Feil, H.: A Clinical Study of the Electrocardiogram

(*Footnote continued on next page*)

intake or absorption, and (3) experimental work on vitamin-deficient diets in animals [3] and a few experiments on human subjects.[4]

The Japanese literature as early as 1886 is said to contain reports of cardiac dysfunction associated with nutritional deficiencies. Aalsmeer and Wenckebach in 1929 described right-sided heart failure due to beriberi in the Orient. Scott and Herrmann [1b] in 1928 reported heart failure from beriberi among persons in Louisiana who were on vitamin-deficient rice diets. Keefer [1a] in 1930 reported his observations on beriberi heart disease in China. Weiss and Wilkins [2a] in 1937 and others have reported on beriberi heart disease in chronic alcoholism in this country. Acute beriberi heart disease probably is not rare in our large general hospitals, but it is often not recognized. Fischbach [5] in 1948 reported his observations on a group of American prisoners who had been released from Japanese prisons and had been treated five to seven weeks. He commented on the relatively few serious residual cardiac abnormalities and noted considerable improvement during his observation period of about three months. One death from persistent beriberi heart disease in an ex-prisoner of war has been reported,[6] and in this case relapses were apparently related to alcoholism and overexertion.

CLINICAL FEATURES OF BERIBERI HEART DISEASE

The earlier reports stressed cardiac enlargement, enlargement of the right side of the heart, failure of the right side of the heart, edema, and accelerated circulation. Other features reported were rapid development of symptoms, liability to unexpected death, association with polyneuritis and other manifestations of vitamin deficiencies, tachycardia, dyspnea, palpitation, and response to treatment with

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5. Fischbach, W. M.: Cardiac and Electrocardiographic Observations on American Prisoners of War Repatriated from Japan, U. S. Nav. M. Bull. **48**:69 (Jan.-Feb.) 1948.

6. Alleman, R. J., and Stollerman, G. H.: The Course of Beriberi Heart Disease in American Prisoners-of-War in Japan, Ann. Int. Med. **28**:949 (May) 1948.

thiamine hydrochloride and proper diet. However, the picture has frequently been found to be atypical, and nearly every cardiac symptom and sign has been reported at some time. These have included orthopnea, precordial pain, both right- and left-sided heart failure, sudden or gradual onset, relapse after apparent recovery, bradycardia, valvular incompetence, vasomotor instability, arrhythmias, gallop rhythm, both rapid and prolonged circulation time, pistol-shot sound over the large arteries, dilated arterioles, venous engorgement, increased capillary permeability, warm skin, anemia, low basal metabolism, behavior disorders, and low serum proteins.

Blankenhorn [2d] has listed his criteria for Occidental beriberi heart disease as follows: (1) enlarged heart with normal rhythm, (2) dependent edema, (3) elevated venous pressure, (4) peripheral neuritis or pellagra, (5) nonspecific electrocardiographic changes, (6) no other evident cause, (7) gross deficiency of diet for three months or more, and (8) improvement and reduction in size of the heart on treatment or autopsy observations consistent with beriberi.

Beriberi heart disease may complicate heart disease of other origin.

The commonest electrocardiographic abnormalities have been low voltage of the QRS complexes, low voltage or inversion of T waves, and prolonged electrical systole. Other observations have been tachycardia, bradycardia, premature contractions, auricular fibrillation, both left axis deviation and right axis deviation, prolonged P-R interval, bundle branch block, slurring of the QRS complexes, and both elevated and depressed S-T segments. There has been a tendency for the electrocardiogram to return to normal on treatment.

PATHOLOGIC STUDIES

The histologic observations on beriberi heart disease have not been specific for this disease, and sometimes no microscopic changes have been seen. The abnormalities most commonly described have been hypertrophy, dilatation, hydropic degeneration of fibers, interstitial edema, replacement fibrosis, a loss of striation of the myocardial fibers, and lymphocytic and leucocytic infiltration. Other observations have been petechial hemorrhage of the endocardium, fibrosis of the endocardium,[7] mural thrombi,[8] pulmonary conus involvement, fatty infiltration, increase in collagen, degeneration of the conduction system, sarcolysis, cloudy swelling, fragmentation, and nuclear degeneration. A similarity to acute isolated (Fiedler's) myocarditis has been noted by some observers. There have also been described degenerative lesions of the nervous system, including the peripheral nerves, vagus nerves, spinal cord tracts, and the sympathetic nervous system.

It has been shown that the increased weight of the heart is not due to water but is presumed to be due to collagen. The peripheral edema has been said to be due to neuritis and usually has preceded the cardiac failure, but cardiac edema may be superimposed. Low serum protein may or may not be a factor. There have been discussions in the literature on whether beriberi heart disease is actually a disease of the myocardium or is a result of widespread peripheral neuritis. It has been

7. Smith, J. J., and Furth, J.: Fibrosis of Endocardium and Myocardium with Mural Thrombosis: Notes on Its Relation to Isolated (Fiedler's) Myocarditis and to Beriberi Heart, Arch. Int. Med. **71**:602 (May) 1943.

8. Dock, W.: Marked Cardiac Hypertrophy and Mural Thrombosis in the Ventricles in Beriberi Heart, Tr. A. Am. Physicians **55**:61, 1940.

proposed that neuritis of the vagus nerve may be partially responsible for the cardiac symptoms. It has also been proposed that the cardiac failure is secondary to the widespread edema. There is some evidence that deficiencies of nicotinic acid, pyridoxine, and vitamins C, A, and D also are factors in cardiac damage.[9] The role of electrolyte disturbances, particularly potassium deficiency, has not yet been determined. Electrocardiographic changes and myocardial necrosis and scarring have been produced in animals by diets deficient in potassium. It has been suggested that in beriberi there is a capillary and arteriolar dilatation which produces a collapsing pulse and heart failure by a mechanism similar to that in arteriovenous fistula. Beriberi heart disease probably results from combinations of myocardial, neurological, peripheral vascular, electrolytic, and protein disturbances.

MATERIAL

Between October, 1945, and August, 1951, one hundred nine men who had suffered from beriberi and severe malnutrition as Japanese prisoners of war were admitted to the United States Public Health Service Hospital, Seattle, for examination and for treatment of any disease determined to have been incurred during imprisonment. These men had been civilian construction workers. All but seven were captured on Wake Island, Dec. 23, 1941; one was captured on Guam, and six were captured in the Philippine Islands. They were released from prison in August, 1945. They had all had preemployment physical examinations and were presumed to have been in good health before going to the islands. After release from prison, all the men were given adequate diets and intensive vitamin therapy for several weeks, and many have continued intermittent vitamin therapy for several years.

The conditions of their imprisonment and deficient diets amounted to an experiment in human malnutrition. During their 44 months of imprisonment they subsisted on a diet grossly deficient in calories and vitamins. The average daily diet consisted of a teacup of half-polished rice and a cup of watery soup three times a day. They were given about 1 spoon of meat a month and fish or fishheads once or twice a month. The fish was usually spoiled and often was not eaten. Sometimes barley or corn was given instead of rice. Occasionally, soybeans or a local vegetable was given. Toward the end of the war a few Red Cross food boxes were distributed. An additional factor in their malnutrition was the fact that they were required to perform hard labor and were subjected to indignities and punishment. There was little or no medical care. It was felt by the group that as civilians who took up arms against the enemy they were treated worse than military prisoners. Of 1,132 of these civilians on Wake Island, only 650 lived to return to the United States. Forty-one were killed during the attack, 100 were executed, and 341 died of diseases. Accurate information is not available on the causes of death, but the men believe that starvation, malnutrition, and pneumonia were the common causes. Thirty-nine of this group died from the time of their return to the United States through 1949. The causes of these deaths were poorly substantiated.

During their imprisonment they all suffered severe malnutrition and weight loss, most of them losing between 45 and 65 lb. (20.4 and 29.5 kg.). The highest weight loss reported was 115 lb. (52.1 kg.). Estimates of weight were complicated by edema. Of the 109 men, 85 gave histories of beriberi recognized in prison. Others may have had beriberi, but information was not recorded on the charts. Some of the men stated that "nearly all" or "98%" had beriberi while in camp. (Hibbs[10] reported that of 8,000 men captured on Bataan all had some form of beriberi at some time.) Of the 109 men, 18 gave specific histories of pellagra, 5 of scurvy, 9 of amebic dysentery, 60 of nonspecific dysenteries, 43 of malaria, 12 of hepatitis or jaundice, and 13 of intestinal worms. Other conditions commonly reported were pneumonia, dental caries, eye diseases and infections (some of which may have been vitamin A deficiencies), and skin ulcers. Many received injuries. For 10 of the men the diagnosis of heart disease was made in

9. Saphir, O.: Myocarditis: A General Review, with an Analysis of 240 Cases, Arch. Path. **32**:1000 (Dec.) 1941. Footnote 2 *n*, *o*, and *t*; 3 *b*.

10. Hibbs, R. E.: Beriberi in Japanese Prison Camp, Ann. Int. Med. **25**:270 (Aug.) 1946.

prison or upon release. One of these probably had rheumatic heart disease; one probably had emphysema, and the rest were assumed to have beriberi heart disease. It is probable that some of the men died of beriberi heart disease in prison, and some may have died of heart disease since release.

It is believed that these men are fairly representative of the survivors. Some came to the hospital with minor complaints, for dental care, for eye examinations, or simply for evaluation. The ages of these men when last examined at this hospital ranged from 25 to 69 years. There were 11 men between the ages of 25 and 29; 44 between the ages of 30 and 39; 30 between the ages of 40 and 49; 16 between the ages of 50 and 59, and 8 between the ages of 60 and 69. Some of the men were examined as many as six times during the six years. Many were hospitalized for weeks at a time. Various diagnostic studies and treatments were carried out, and operative procedures were performed as indicated. Two of the men died at this hospital, and autopsies were performed on both of them.

RESULTS

The significant cardiovascular findings are given in the Table. On physical examination nine of the men were found to have systolic heart murmurs. No diastolic murmurs were heard. Five of the murmurs were at the apex; one was at the pulmonic area; two were both aortic and apical, and one was generalized over the precordium. In only two of these nine men with murmurs was there other evidence of heart disease. Other observations on cardiovascular examination were as follows: In one man the pulmonic second sound was greater than the aortic second sound; one man had a split apical first sound, and one man had an accentuated aortic second sound. In general, the heart rates were well within normal limits, those of only five men being considered abnormal: Three of these had tachycardia associated with hypertension, and two had bradycardia (a 56-year-old man with arteriosclerosis had a heart rate of 44, and a 53-year-old man had a heart rate varying between 40 and 80).

Eleven of the men had blood-pressure readings which exceeded normal limits on one or more determinations. Six of these were believed to have organic cardiovascular or vascular disease. The other five were believed to be hypertensive reactors. One 34-year-old man had a blood pressure of 98 systolic and 60 diastolic, which was believed to be of no clinical significance.

Chest roentgenograms were taken on 96 of the 109 men. Three men were found to have enlarged hearts, of whom one died of uremia and hypertension, one had arteriosclerotic heart disease, and one had rheumatic heart disease. Other men with abnormalities on chest roentgenogram were as follows: One 59-year-old man showed calcification of the aorta; one 61-year-old man had a widened aorta; one 46-year-old man showed a prominence of the heart shadow near the pulmonary conus; one 57-year-old man had a prominent and calcified aortic knob; one 64-year-old man showed sclerosis of the thoracic aorta. None of the 109 men were believed to have enlargement of the heart due to beriberi heart disease.

One or more electrocardiograms were taken for 81 of the men. Early in the study tracings with the three standard limb leads and a CF_4 lead were done; later tracings with the standard leads, the augmented unipolar limb leads, and the six precordial leads were done. Six men were found to have abnormal electrocardiograms as follows: The first man showed anterior myocardial infarction; a 53-year-old man with arteriosclerotic heart disease had right bundle branch block; a man with rheumatic heart disease had an inverted T wave in Lead I, diphasic T wave in

Summary of Cardiologic Data on 109 Men with Beriberi and Malnutrition

Case No.	Age When Last Seen	Dates First and Last Seen	Diseases While in Prison	Principal Diagnoses	Pulse Rate	Blood Pressure	Results of Physical Examination of Heart	Roentgenogram of Heart*	Electrocardiogram*					Comment
									Rate on ECG	Q-T Interval Sec.	Maximum R Wave in Limb Leads, Mm.	Maximum T Wave in Limb Leads, Mm.	Other ECG Findings	
1	30	1/15/51 2/ 8/51	Beriberi, dysentery, malaria, jaundice, ascariasis	Essential hypertension	72	175/100	Normal	Normal	79	0.36	13	2	.....	.....
2	30	5/31/49 6/16/49	Beriberi, dysentery	Post-traumatic encephalopathy	74	120/80	Normal	Normal	74	0.36	17	3	.....	Serum protein, 6.2 gm.
3	31	2/17/50 11/11/50	Beriberi, malaria	Old bullet wound, right elbow	72	110/65	Normal	Normal	60	0.38	10	4	.....	.....
4	46	1/18/51 1/25/51	Beriberi, "fever"	Refractive error, eyes	72	135/80	Normal	Normal	66	0.36	11	2	.....	.....
5	57	5/14/47 1/23/51	Beriberi, dysentery, pneumonia	Osteoarthritis, chronic bronchitis	68-82	110/68 130/90	Normal	Normal	70	0.38	8	2	.....	Vital capacity, 71% of normal; circulation time, 15 sec.
6	37	1/23/51 1/30/51	Malaria, dysentery, jaundice	Renal calculus	72	150/70	Normal	Normal	104	0.30	9	2.5	RAD†	Pyuria
7	34	2/14/49 5/ 7/49	Beriberi, pellagra, osteomyelitis, nocturia	Glomerulonephritis, chronic and subacute	80-120	190/115	Enlargement; loud A_2	Globular heart	80	0.36	15	3	.....	Died of uremia, terminal pericarditis, bronchopneumonia
8	45	2/ 3/49 2/15/49	Amebic dysentery	Osteoarthritis	84	140/82	Normal	Normal	—				.....	.....
9	41	1/30/51 3/30/51	Beriberi, pellagra	Ingrown toenail	88	110/60	Normal	Normal	81	0.36	10	1.5	.....	Chief complaint: chronic fatigue
10	36	2/19/51 3/ 2/51	Beriberi	Biliary dyskinesia	64	100/90	Normal	Normal	64	0.36	13	3	.....	.....
11	36	3/13/51 4/ 7/51	Beriberi, ascariasis, goiter	Traumatic arthritis of hip	76	120/80	Normal	Normal	63	0.38	14	3	.....	Thyroidectomy, 1946
12	32	4/ 4/51 4/25/51	Beriberi, dysentery, asthma	Porphyria	78	144/90	Normal	Normal	78	0.36	18	2.5	.....	Tachycardia and edema until Dec., 1945
13	33	2/15/51 2/24/51	Beriberi, pellagra, malaria, dysentery	Old fractures, arm	64	118/70	Normal	Normal	63	0.36	12	3.5	.....	Polyneuritis until Feb., 1946
14	47	2/18/49 3/10/51	Beriberi, leg ulcers, "eye trouble"	Osteoarthritis	76	120/70	Normal	Normal	80	0.36	5	1.5	.....	Serum protein, 7 gm.
15	30	1/22/51 2/ 8/51	Beriberi, scurvy, malaria, leg ulcers	Dental caries	72	140/82	Normal	Normal	64	0.36	13	3.5	.....	Pains in legs
16	57	4/27/49 5/26/49	Chills and fever, dysentery, cellulitis	Cholelithiasis	70	144/110	Normal	Aortic nob prominent and calcified; heart normal	ECG normal; tracing lost				.....	Circulation time, 14 sec.; vital capacity, 95%
17	44	4/ 4/51 5/22/51	Beriberi, malaria	Osteoarthritis, anxiety	80	110/60	Normal	Normal	72	0.34	10	3	.....	.....
18	58	5/ 7/51 5/18/51	Beriberi, hernia	Abdominal hernia, osteoarthritis	64	110/78	Normal	Normal	72	0.34	6.5	0.75	Low T waves in limb leads; normal precordial leads	Dyspnea on exertion; history of ankle edema
19	58	4/26/51 5/15/51	Malaria, diarrhea, dental caries	Neurasthenia	88	125/75	Normal	Normal	78	0.32	3.5	2	Low QRS complexes	.....
20	60	5/ 7/51 6/ 4/51	Beriberi, dysentery, ? stroke	Myocardial infarction, old; angina	76	130/80	Normal	Heart moderately enlarged to left	92	0.34	5	2	Old anterior infarction by ECG	History of infarction, Nov., 1949

21	53	10/21/46 11/12/46	Beriberi, dysentery, heart disease	Arteriosclerotic heart disease	64	124/70	Heart normal; asthma	Normal	72	0.40	9	4	Right BBB‡	Circulation time, 12 sec.; heart disease antedated beriberi
22	46	1/16/47 1/28/47	Beriberi, dysentery	Asthma, hypochondriasis	60-90	138/90	Systolic apical murmur	Normal	72	0.36	18	4	.....	Asthma and emphysema
23	25	4/10/46 4/16/46	Beriberi, dysentery, malaria, "eye trouble"	No disease	68	125/90	Normal	Normal	72	0.38	18	2.5	.....	Wet beriberi until Oct., 1945
24	63	8/29/50 9/ 7/50	Beriberi, dysentery, malaria, "eye trouble"	Chronic prostatitis	80	132/76	Soft apical systolic murmur	—	—				.....	.....
25	30	4/ 9/47 5/25/47	Beriberi, dysentery, pellagra, malaria	No disease	66	120/76	Systolic murmur	Normal	—				.....	Positional murmur
26	36	11/20/47 12/18/47	Beriberi, dysentery	Amebic colitis	68	125/95	Normal	Normal	66	0.36	11.5	3	.....	.....
27	32	8/17/50 8/23/51	Beriberi, malaria	Hypothyroidism	60	98/68	P_2 greater than A_2	Normal	54	0.40	8.5	4	.....	B. M. R. —27%; serum cholesterol, 304 mg.
28	45	1/ 3/47 11/ 5/47	Beriberi, dysentery, malaria	Multiple sclerosis	80	120/80	Normal	Normal	—				.....	.....
29	37	7/ 5/46 8/31/49	Beriberi, pellagra, amebic dysentery, worms	Sinusitis, deafness	82	120/88	Normal	Normal	80	0.36	10	2	Slight RAD	.....
30	44	11/17/49 12/ 3/49	Beriberi, diarrhea	Rheumatoid arthritis	80	125/90	Normal	Normal	90	0.32	12	2	One ectopic ventricular beat	.....
31	35	9/ 3/47	Beriberi, jaundice, poor vision	No disease	60-80	125/80	Normal	Normal	60	0.36	13	2.5	.....	B. M. R. —12%
32	59	9/10/45	Beriberi, sprue, malaria, foot drop	Arteriosclerosis; chronic bronchitis	76	124/72	Normal	Calcified aorta; heart normal	69	0.36	9	2.5	.....	Circulation time, 13 sec.; vital capacity, 75% of normal; arteriosclerosis obliterans
33	39	4/26/46 4/11/51	Beriberi, scurvy, dysentery, pneumonia	Amebic colitis, chronic bronchitis	72	120/70	Normal	Normal	67	0.36	9	3	.....	Pleural adhesions by roentgenogram
34	60	6/ 7/50 7/15/50	Beriberi, dysentery, dengue	Arteriosclerotic and hypertensive cardiovascular disease	72	220/110	Apical and aortic systolic murmur	Normal	95	0.30	12	0	Digitalis effect; ectopic ventricular beats	Circulation time, 20 sec.; vital capacity, 53% of normal; loud A_2
35	38	3/15/49 3/22/49	Beriberi, pellagra	Postencephalitic Parkinsonism	80	130/80	Normal	—	72	0.40	12	3	.....	Onset of Parkinsonism, 1925
36	31	2/27/47 4/30/51	Beriberi, pellagra, hepatitis, dysentery	No disease	76	135/70	Normal	Normal	78	0.36	17	3	Sinus arrhythmia	Diagnosed heart disease, Aug., 1946
37	61	6/20/46 2/11/48	Beriberi, pneumonia	Duodenal ulcer, giardiasis, arthritis	60	130/70	Normal	Normal	52	0.40	11	2.5	.....	Circulation time, 15 sec.
38	41	9/29/47 11/17/47	Beriberi, pellagra, dysentery, ascariasis	Unstable knee ligaments; rheumatic heart disease	80	124/80	Normal	Normal	75	0.36	10	0.5	Inverted T_1, diphasic T_3, LAD,§ absent R_4	Acute rheumatic fever and pericarditis, Jan., 1946
39	41	6/28/46 7/18/46	Beriberi, malaria	Psychoneurosis	78	130/80	Normal	—	76	0.34	13	2	.....	B. M. R. —12%
40	37	5/25/49 6/11/49	Beriberi, malaria, dysentery, jaundice	Asthma, sinusitis	72	144/86	Normal	Normal	56	0.38	20	3	.....	.....
41	44	1/14/46 1/26/46	Beriberi, malaria, dysentery, worms	Chronic bronchitis	70	120/85	Normal	Normal	76	0.36	7	3	QRS, 0.10 sec.	.....
42	39	7/28/47 7/20/48	Beriberi, scurvy, dysentery, pneumonia, hepatitis	Cirrhosis of liver	80	118/70	Normal	Normal	—				.....	Hemoglobin, 12.8 gm.; serum protein, 5.3 gm.; autopsy showed postinfectious cirrhosis of liver and myocardial fibrosis
43	50	11/24/47 1/ 2/48	Pellagra, diarrhea	Hemorrhoids, presbyopia	88	120/82	Normal	Normal	86	0.34	15	3.5	.....	Hemoglobin, 18.3 gm.; R. B. C., 6,230,000

Summary of Cardiologic Data on 109 Men with Beriberi and Malnutrition—Continued

Case No.	Age When Last Seen	Dates First and Last Seen	Diseases While in Prison	Principal Diagnoses	Pulse Rate	Blood Pressure	Results of Physical Examination of Heart	Roentgenogram of Heart*	Electrocardiogram* Rate on ECG	Q-T Interval Sec.	Maximum R Wave in Limb Leads, Mm.	Maximum T Wave in Limb Leads, Mm.	Other ECG Findings	Comment
44	36	9/25/50 10/ 7/50	Dysentery	Hypertensive vascular disease	84-88	160/115	Normal	Normal	69	0.36	9.5	2	QRS 0.10 sec.; slight notching R_2 and R_3	Nonexertional precordial pain
45	33	5/16/49 4/25/50	Beriberi	Duodenal ulcer	76	120/85	Normal	Fluoroscopy normal	54	0.40	7	2.5	.....	Occasional premature beats
46	32	11/14/50 11/17/50	Beriberi, malaria, diarrhea, "flu"	Anxiety state	86	110/85	Normal	Normal	62	0.36	10	2	.....	Hemoglobin, 17.8 gm.; aching in legs
47	52	8/25/49 9/ 4/49	Diarrhea, ? beriberi, "irregular heart beat"	Deviated nasal septum	64	140/85	Normal	Normal	Normal except ectopic ventricular beats					Suspected heart disease in prison; circulation time, 35 sec. ??
48	33	7/10/47 7/17/47	Beriberi, pellagra, asthma	No disease	76	105/68	Normal	Normal	70	0.36	14	3	.....	B. M. R., +2%; serum protein, 7.7 gm.
49	46	9/ 8/48 5/25/51	Beriberi, pellagra, malaria, dysentery	Arthritis, sprue	76	140/88	Normal	Normal	84	0.32	9	2.5	Slight LAD	B. M. R., —4%
50	28	5/26/47 6/19/47	Malaria, dysentery, pneumonia	Pyorrhea	80-82	120/85	Apical systolic murmur	Normal	—				.....	No cardiovascular symptoms
51	65	12/ 7/48 4/ 1/50	Beriberi, respiratory infections	Hypertensive vascular disease, otitis media	40-80	150/90 200/100	Normal; premature beats	Normal	55 75	0.40 0.36	11 11	1 3	Digitalis effect	Circulation time, 16 and 18 sec.; vital capacity, 87% of normal; serum protein, 7 gm.
52	34	5/28/48 8/ 4/48	Diarrhea, jaundice, cough	Perirectal abscess, sinusitis	80	110/70	Normal	Normal	—				.....	.....
53	30	11/21/49 6/11/51	Beriberi, pellagra, dysentery, fever	No disease	80	125/75	Normal	Normal	80	0.32	9	2	.....	B. M. R., —10%
54	61	2/12/46 11/28/50	Beriberi, diarrhea, bad teeth	Diabetes, obesity, hypertensive vascular disease	80-94	140/95 168/110	Loud A_2	Heart normal, ? wide aorta	94	0.32	9	2.5	.....	Blood pressure "160" before war
55	26	5/14/47 5/22/47	Dysentery	No disease	72	110/70	Normal	—	—				.....	.....
56	60	12/ 8/46 11/21/50	Malaria	Arterioscleroticheart disease, chronic bronchitis	64	132/76	Split apical 1st sound	Normal	72	0.36	13	2	Normal on Master's test	Asthma prior to war; B. M. R. —12%; circulation time, 17 sec.
57	40	7/ 9/47 3/20/50	Malaria, diarrhea	Anxiety state, alcoholism	84	128/80	Normal	Normal	76	0.36	18	3	.....	Serum protein, 6.6 gm.; serum cholesterol, 333 mg.
58	29	11/10/50 11/15/50	Malaria, dysentery	Old bullet wound and fracture of arm	64	135/80	Normal	Normal	62	0.36	10	3	.....	.....
59	34	1/13/47 8/11/47	Beriberi, dysentery, pneumonia, abscesses	Pyelonephritis	80	138/86	Normal	Normal	—				.....	.....
60	50	11/15/45 11/21/45	Not recorded	Deflected nasal septum	64	140/85	Normal	—	—				.....	.....
61	52	11/29/47 6/28/50	Beriberi, malaria, amebic dysentery	Amebiasis; scar, left leg	80	140/90 176/106	Normal	Normal	72	0.36	9	3	.....	Circulation time, 25 sec. (?)
62	35	4/27/50 5/11/50	Beriberi, pneumonia	Allergic rhinitis	72	120/78	Normal	Normal	55	0.44	18	2.5	.....	.....
63	37	1/ 7/46 12/14/50	Jaundice	Old injury to finger, hydrocele	76	122/78	Normal	Normal	67	0.36	14	2	.....	.....

64	38	11/13/50 11/22/50	Beriberi (neuritis), malaria	Osteoarthritis	72	125/75	Normal	Normal	60	0.36	7	2	.....	.....
65	27	2/24/47 3/14/47	Dysentery, worms	Hypothyroidism	56-60	135/70	Normal	—	—				.....	B. M. R., —18%
66	30	5/17/47 6/16/47	Amebic dysentery, malaria, empyema	Amebic colitis	72	130/70	Normal	Normal	—				.....	Pleural adhesions
67	42	3/26/47 4/ 9/47	Not recorded	Arthritis of spine	68	120/74	Normal	Normal	—				.....	.....
68	59	9/16/47 10/13/47	Beriberi, malaria	Ventral hernia	56-78	125/75	Normal; ectopic beats	Normal	60	0.38	12	2	Ectopic ventricular beats	Beriberi worse after liberation
69	47	11/ 6/45 12/ 5/45	Beriberi, amebic dysentery	Incisional hernia	64	132/74	Normal	—	—				.....	.....
70	44	10/12/48 1/24/50	Beriberi, pellagra, dysentery	Osteoarthritis of spine	72	120/80	Normal	Normal	58	0.36	9	2	.....	.....
71	42	2/ 2/46 3/18/50	Beriberi, pellagra	Ureteral stricture	75	110/78	Normal	Normal	—				.....	.....
72	44	10/27/45 4/15/49	Beriberi, malaria, dysentery, arthritis	Retrobulbar neuritis, fissure in ano	80	134/70	? Systolic murmur, aortic, mitral	Normal	86	0.34	10	2	.....	Circulation time, 13 sec.; serum protein, 6 gm.
73	32	10/11/50 1/31/51	Beriberi, amebic dysentery, back injury	Pseudarthrosis in lumbosacral fusion	80	128/84	Normal	—	—				.....	.....
74	32	5/30/46 6/ 8/46	Beriberi, pellagra, malaria, dysentery	Leukoma	80	142/90	Normal	Normal	Reported normal, 1945				.....	.....
75	49	2/13/46 2/25/46	Beriberi, pellagra, dysentery, pneumonia	Chronic bronchitis	72	120/92	Normal	Normal	—				.....	2+ Kahn reaction
76	36	1/ 8/50 1/17/50	Malaria, dysentery	Duodenal ulcer	72	108/66	Normal	Normal	—				.....	.....
77	56	1/ 8/48 5/14/50	Beriberi, dysentery, fractured ribs	Arteriosclerosis obliterans	42-60	110/75	Normal	Normal	44	0.44	11	4	P-R, 0.12 sec.	Circulation time, 17 sec.
78	46	11/10/46 3/24/49	Beriberi, rheumatic fever	Rheumatic heart disease, inactive	66-88	118/72	Systolic apical murmur, heart enlarged	Heart shadow widened	76	0.36	12	3	Normal ECG	Circulation time, 16 sec.; rheumatic fever while in prison
79	28	1/ 9/46 2/16/46	Malaria, dysentery	Cholelithiasis	72	130/68	Normal	—	—				.....	.....
80	26	2/12/47 3/ 1/47	Beriberi, malaria, dysentery	Diabetes, bursitis	80	110/74	Normal	—	—				.....	.....
81	38	12/ 1/47 3/25/48	Beriberi, malaria, dysentery	Old fracture, leg	80	112/80	Soft systolic pulmonic murmur	Normal	—				.....	.....
82	38	12/21/48 11/13/50	Malaria, jaundice, pneumonia	Nerve deafness	78	128/80	Normal	Normal	70	0.34	19	3	.....	Myocarditis late in 1945
83	52	4/11/50 4/29/50	Beriberi, blurred vision	Optic atrophy, hernia, neuritis	88	160/100	Normal	—	—				.....	.....
84	30	6/26/47 7/ 4/47	Malaria, dysentery, osteomyelitis	Old fractures, leg and hand	84	120/70	Normal	—	—				.....	.....
85	44	12/ 4/47 9/21/49	Pellagra, scurvy, malaria, pneumonia, amebic dysentery	Spondylolisthesis	84	128/85	Soft apical systolic murmur	Normal	82	0.36	11	3	.....	.....
86	44	3/29/49 8/23/51	Beriberi, pellagra, dysentery, hookworm, pneumonia	Diverticulum of duodenum, neurasthenia	74	120/80	Normal	Normal	65	0.36	7.5	3	.....	Circulation time, 12 sec.
87	43	12/ 2/47 11/25/49	Beriberi, worms	Urethral stricture, hemorrhoids	80	118/78	Normal	Normal	—				.....	.....
88	29	3/15/49 3/29/49	Beriberi, dysentery	Vasomotor instability	80	124/80	Normal	Normal	86	0.32	9	2.5	.....	Circulation time, 15 sec.; vital capacity, 110% of normal
89	40	3/ 8/47 3/18/47	Beriberi heart disease, bacillary dysentery	Deformity of finger due to trauma	78	120/70	Normal	Normal	70	0.36	14	3	.....	Circulation time, 21 sec.; normal exercise tolerance

Summary of Cardiologic Data on 109 Men with Beriberi and Malnutrition—Continued

Case No.	Age When Last Seen	Dates First and Last Seen	Diseases While in Prison	Principal Diagnoses	Pulse Rate	Blood Pressure	Results of Physical Examination of Heart	Roentgenogram of Heart*	Electrocardiogram*				
									Rate on ECG	Q-T Interval Sec.	Maximum R Wave in Limb Leads, Mm.	Maximum T Wave in Limb Leads, Mm.	Other ECG Findings
90	33	9/30/46 7/12/48	Beriberi, pellagra, dysentery, poor vision	Conversion hysteria, ? optic neuritis	76	110/60	Normal	Normal	—				.....
91	36	6/ 9/49 9/20/49	Beriberi, diarrhea, pneumonia	Diverticulum of colon, anxiety state	80	108/74	Normal	Normal	96	0.36	18	6	.....
92	34	1/ 6/46 1/21/46	Beriberi, malaria, hepatitis, worms, poor vision	Herpes zoster, optic atrophy	80	98/60	Normal	Fluoroscopy normal	—				.....
93	43	2/ 2/48 2/20/50	Beriberi, malaria, bad eyes, pleurisy	Rectal polyps, contact dermatitis	76	116/84	Normal	Normal	64	0.36	11.5	3	.....
94	25	6/ 5/46 6/29/46	Malaria, amebic dysentery	Amebic colitis	75	135/70	Normal	—	—				.....
95	33	8/22/49 9/19/49	Beriberi, ascariasis, chills and fever	Chronic colitis, hemorrhoids	76	112/66	Normal	Normal	80	0.36	13	3	.....
96	64	5/11/50 6/ 1/50	Beriberi, dysentery, collapsed lung	Old fracture, lumbar vertebra; basal-cell carcinoma	82	148/78	Normal	Heart normal, sclerosis of aorta	80	0.36	5	1	Diphasic T_4
97	53	5/26/47 6/12/47	Beriberi, worms, abscesses	Osteoarthritis of spine, emphysema	40-80	130/80	Normal	Normal	40	0.44	6	3.5	.....
98	48	12/29/48 1/23/51	Beriberi, malaria, jaundice, infected knee	Postgastrectomy symptoms	72	121/80	Normal	Normal	70	0.34	9	2	.....
99	46	1/ 3/50 1/ 5/50	Beriberi, malaria, pneumonia	Astigmatism, presbyopia	80	135/85	Normal	Prominent pulmonic region	66	0.36	15	2	.....
100	39	7/21/47 7/28/47	Beriberi	Acute bronchitis	68	126/74	Normal	Normal	50	0.40	12	1	.....
101	33	2/ 6/50 3/ 1/50	Beriberi, intestinal parasites	Giardiasis, astigmatism	78	110/70	Normal	Normal	—				.....
102	49	2/ 9/50 2/21/50	Beriberi, jaundice, pleurisy	Fistula in ano, hemorrhoids	84	130/80	Normal	Normal	60	0.36	9	2	LAD; QRS, 0.10 sec.
103	45	3/20/47 4/ 7/47	Beriberi, scurvy, pneumonia, abscesses	Sinusitis, bronchitis	74	112/74	Normal	Normal	60	0.38	13	3	.....
104	35	1/ 9/51 1/17/51	Dysentery	No disease	76	150/85	Normal	Normal	66	0.36	14	1.5	.....
105	29	6/18/51 8/23/51	Beriberi, dysentery	Foreign body in knee	72	138/80	Normal	Normal	78	0.32	6	0.25	T waves low in limb leads, normal in chest leads
106	27	3/10/51 3/11/51	Dysentery, chills and fever	No disease	70	116/80	Normal	Normal	70	0.36	10	3	.....
107	51	6/11/51 6/19/51	Beriberi, malaria, dysentery, worms	Duodenal ulcer, healed	76	140/80	Normal	Normal	75	0.34	8	2.5	.....
108	49	2/ 7/48 3/ 2/48	Beriberi, malaria, dysentery	Conjunctivitis, astigmatism	68	120/75	Normal	Normal	60	0.40	12	3	.....
109	59	7/24/51 8/23/51	Beriberi, dysentery, leg ulcers	Old leg fractures	72	150/90	Normal	Normal	70	0.36	9	3	.....

Case No.	Comment
90	.....
91	.....
92	.....
93	Record of beriberi heart disease, Sept., 1945; serum protein, 7.4 gm.
94	.....
95	.....
96	Dyspnea on exertion; obese; arteriosclerosis; probable mild arteriosclerotic heart disease
97	.....
98	Circulation time, 16 sec.
99	Beriberi heart disease, Oct., 1945; serum protein, 7.3 gm.
100	.....
101	.....
102	.....
103	.....
104	.....
105	.....
106	.....
107	Record of giardiasis
108	Palpitation with beriberi in prison
109	.....

* Minus sign indicates no study made.
† RAD indicates right axis deviation.
‡ BBB means bundle branch block.
§ LAD indicates left axis deviation.

Lead II, and left axis deviation; a man with hypertensive vascular disease had a QRS interval of 0.10 second and abnormal notching of R waves in Leads II and III; a man with arteriosclerotic heart disease had flattened T waves and depressed S-T segments, and a 64-year-old man had a borderline abnormal diphasic precordial T wave. In addition to these six, one tracing showed digitalis effect; one revealed bradycardia, two showed flattened T waves in limb leads only, one disclosed low voltage of the QRS complex (3.5 mm.), and three showed ectopic ventricular beats. In all the other electrocardiograms the voltage of the QRS complex was within normal limits (the R wave in standard limb lead was 5 mm. or over), the Q-T interval was within normal limits (according to Ashman and Hull's table [11]), and the T waves were normal.

Arm-to-tongue circulation times were determined for 16 of the men. In seven of the men the circulation time exceeded normal limits. Two of these had arteriosclerotic heart disease; one had hypertension. In general, there was poor correlation between the circulation time and the other evidence of heart disease, probably due to failure to repeat the test.

Standard Kahn tests were done on all the men, and all the reactions were negative except for one 2+ positive reaction. Hemoglobin determinations were done on all the men, and in only two was the level below normal, in one man who died of uremia and in one with an unexplained hemoglobin level of 12.9 gm. per 100 cc. In general, the hemoglobin levels were high normal. The serum proteins were determined for nine men, and in all but two were well within normal limits; one of these men died of cirrhosis of the liver; in the other the examination was made soon after his release from prison. Results of various other diagnostic procedures if normal or not related to the cardiovascular system are not recorded in this report.

An analysis of the 109 cases shows the following cases of cardiovascular disease:

A. Definite Heart Disease

1. Myocardial infarction and angina pectoris in a 60-year-old man who had an anterior infarction in November, 1949 (Case 20)
2. Arteriosclerotic heart disease in a 53-year-old man who had asthma two days after capture, had dyspnea on exertion, and was digitalized while in prison; his electrocardiogram showed right bundle branch block (Case 21)
3. Arteriosclerotic and hypertensive cardiovascular disease in a 69-year-old man who had a blood pressure of 220 systolic and 110 diastolic; his electrocardiogram showed only digitalis effect (Case 34)
4. Inactive rheumatic heart disease in a 46-year-old man with a history of rheumatic fever while in prison who was found to have a soft systolic mitral murmur; his roentgenogram showed a widened heart; his electrocardiogram was normal (Case 78)
5. Inactive rheumatic heart disease in a 41-year-old man with a history of rheumatic fever and pericarditis after release from prison; there were no murmurs; his electrocardiogram showed low T waves and at one time an inverted T wave in Lead I (Case 38)

B. Probable Heart Disease

1. A 64-year-old man with arteriosclerosis was short of breath on exertion; the roentgenogram of his chest showed sclerosis of the thoracic aorta; the electrocardiogram showed a diphasic T wave in the precordial lead (Case 96)

11. Ashman and Hull, in Burch, G. E., and Winsor, T.: A Primer of Electrocardiography, Ed. 2, Philadelphia, Lea & Febiger, 1949, p. 219, Table 5: Normal QT Intervals.

2. A 60-year-old man had typical symptoms of angina pectoris; the electrocardiogram and result of Master's test were normal (Case 56)
3. A 58-year-old man had shortness of breath on exertion and occasional ankle edema; the electrocardiogram showed flat T waves in Leads I, II, and III (Case 18)

Other cases of vascular disease without heart disease were as follows:

1. A 61-year-old man with diabetes had a blood pressure of 168 systolic and 110 diastolic; he gave a history of blood pressure readings of "160" before imprisonment (Case 54)
2. A 65-year-old man had blood pressure readings varying from 150 systolic and 90 diastolic to 200 systolic and 100 diastolic (Case 51)
3. A 36-year-old man had a blood pressure of 160 systolic and 115 diastolic (Case 44)
4. A 59-year-old man with arteriosclerosis obliterans had calcification of the aorta on roentgenogram (Case 32)
5. A 56-year-old man had arteriosclerosis obliterans and a heart rate of 42 to 60 per minute (Case 77)
6. A 57-year-old man had calcification of his aorta, shown on the roentgenogram (Case 16)

Two men had suggestive cardiac symptoms, but it was concluded that the symptoms were of functional origin (Cases 98 and 102).

The two men who died and were autopsied had abnormalities of the heart which will be discussed later (Cases 7 and 42).

It was found that 101 of the 109 men, or 92.7%, had no clinical evidence of heart disease, and 95, or 87.1%, had no significant cardiovascular disease. Eight of the 108 men, or 7.3%, had definite or probable heart disease. With division into age groups, 2 of the 30 men between the ages of 40 and 49, or 6.7%; 2 of the 16 men between the ages of 50 and 59, or 12.5%, and 4 of the 8 men between the ages of 60 and 69, or 50%, had heart disease. In all the cases of heart disease the causation was believed to be arteriosclerosis, rheumatic fever, or hypertension, and in none of the cases was there any clinical evidence of residual beriberi heart disease.

COMMENT

In order to compare the incidence of heart disease in this group of men with that in the general population, an effort was made to find the expectancy of heart disease among men of different age groups. Most statistics available are on special groups and are subject to a number of variable factors and possible errors. The largest statistical group found was that of Collins [12] taken from a National Health Survey done in 1935 and 1936. He reported the results of a house-to-house canvass covering 2,500,000 persons of all ages in 83 cities in 18 states. This was done by inquiry alone, and it was noted that many more cases probably would have been found by even a superficial examination. His approximate figures for heart disease among men of various age groups were as follows: ages 25 to 29, 0.5%; ages 30 to 34, 0.6%; ages 35 to 39, 1.0%; ages 40 to 44, 1.5%; ages 45 to 49, 1.8%; ages 50 to 54, 2.3%; ages 55 to 59, 3.8%; ages 60 to 64, 5.4%; ages 65 to 69, 7.3%. A survey of life insurance examinations was cited, in which 4.6% of 100,000 men, aged 20 to 69, had organic heart disease. Another survey of 10,000 industrial

12. Collins, S. D.: Statistical Studies of Heart Disease: V. Illness from Heart and Other Cardiovascular-Renal Diseases Recorded in General Morbidity Surveys of Families, Pub. Health Rep. **64**:1439 (Nov. 18) 1949.

workers showed that 4.2% of men between the ages of 20 and 59 had heart disease. Approximately 2% of selective-service registrants between the ages of 18 and 37 were rejected in World War II for cardiovascular defects.[13] A Farm Security Administration survey among low-income groups found that 6.5% of the men between the ages of 30 and 34 and up to 22% of the men between the ages of 60 and 64 had heart disease.

It is difficult to draw any comparison between the above statistics and findings in the group under study. This group of men was examined before employment and found to be free of apparent heart disease. They may represent a group of men who were hospitalized because they believed they had some illness. They may represent the survivors of the group. A more thorough search for heart disease was made in these men than was possible in the above surveys.

One case (Case 42) warrants comment because of an unusual myocardial fibrosis seen on postmortem examination. This man was hospitalized twice between July, 1947, and the time he died, July 20, 1948, at the age of 39. The cause of death was cirrhosis of the liver. During his imprisonment, he had beriberi, scurvy, dysentery, and pneumonia, and in 1945, while still in prison, he contracted hepatitis. He remained jaundiced from this time until his death. During the time he was out of the hospital, he drank alcohol excessively for periods. There were also periods when he was vomiting and his diet was inadequate. When examined, he was febrile and deeply jaundiced (serum bilirubin of 24 to 30 mg. per 100 cc.). The heart was normal on physical examination. The blood pressure was 118 systolic and 70 diastolic. The pulse rate varied from 60 to 100 per minute. A roentgenogram of the chest was normal. An electrocardiogram was not taken. In spite of intensive dietary and vitamin therapy, his course was progressively downhill and he died three years after the onset of hepatitis. On postmortem examination there were typical postinfectious cirrhosis of the liver, esophageal varices with rupture and hemorrhage into the gastrointestinal tract, ascites, terminal bronchopneumonia, and cloudy swelling of the kidneys. The heart weighed 300 gm. and was not remarkable grossly. The valves, coronary arteries, and pericardium were normal. The microscopic examination showed a definite patchy focal fibrosis of the myocardium (Figs. 1 and 2) scattered through areas of normal myocardium. One pathologist believed some sections showed degeneration of muscle fibers, loss of nuclei, loss of striations, and edema. Another pathologist believed these changes were the result of the technique in preparing the sections. All observers agreed, however, that the fibrosis was abnormal. The question arose whether the fibrosis was the result of beriberi or a secondary result of the terminal cirrhosis, which, in spite of treatment, was associated with deficient nutrition, vomiting, ascites, and bleeding. Available medical references do not discuss the occurrence of cardiac lesions in cirrhosis. Weiss and Wilkins [28] in 1937 observed some inconstant, nonspecific myocardial changes at autopsy among patients with nutritional deficiencies, cirrhosis, and organic heart disease and among patients without known heart disease. Wartman and Hellerstein,[14] in reporting on the incidence of heart disease in 2,000 autopsies,

13. Goldstein, M. S.: Physical Status of Men Examined Through Selective Service in World War II, Pub. Health Rep. **69**:587 (May 11) 1951.

14. Wartman, W. B., and Hellerstein, H. K.: The Incidence of Heart Disease in 2,000 Consecutive Autopsies, Ann. Int. Med. **28**:41 (Jan.) 1948.

listed subacute myocarditis in one case of acute hepatic necrosis and in one case of cirrhosis.

The autopsy material on 11 patients who died of cirrhosis of the liver at this hospital was reviewed. In four the hearts were normal; in four the hearts showed only coronary arteriosclerosis; in one, diffuse myocardial swelling; in one, hypertrophy, and in one, extravasation of erythrocytes into the myocardium. None of these hearts showed fibrosis of the myocardium. The problem of myocardial damage secondary to cirrhosis deserves further study.

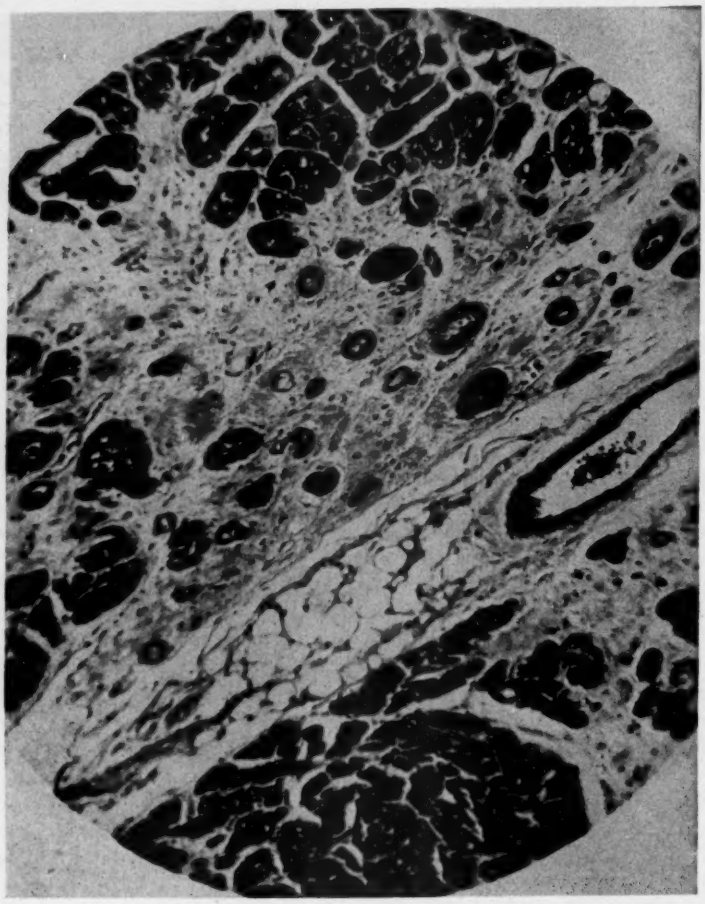

Fig. 1 (Case 42).—Patient died from cirrhosis of the liver. High-power field of myocardium, showing area of patchy fibrosis.

The other patient on whom an autopsy was performed (Case 7) died on May 7, 1949, at the age of 34, of chronic and subacute glomerulonephritis and uremia.

He had beriberi, pellagra, and osteomyelitis while in prison. He gave a history of the onset of nocturia while in prison, and six months prior to death he became progressively ill with fever, malaise, headache, hematuria, edema of the face, and vomiting. On examination the blood pressure was 190 systolic and 112 diastolic. The blood urea nitrogen was found to be as high as 82 mg. per 100 cc. On post-

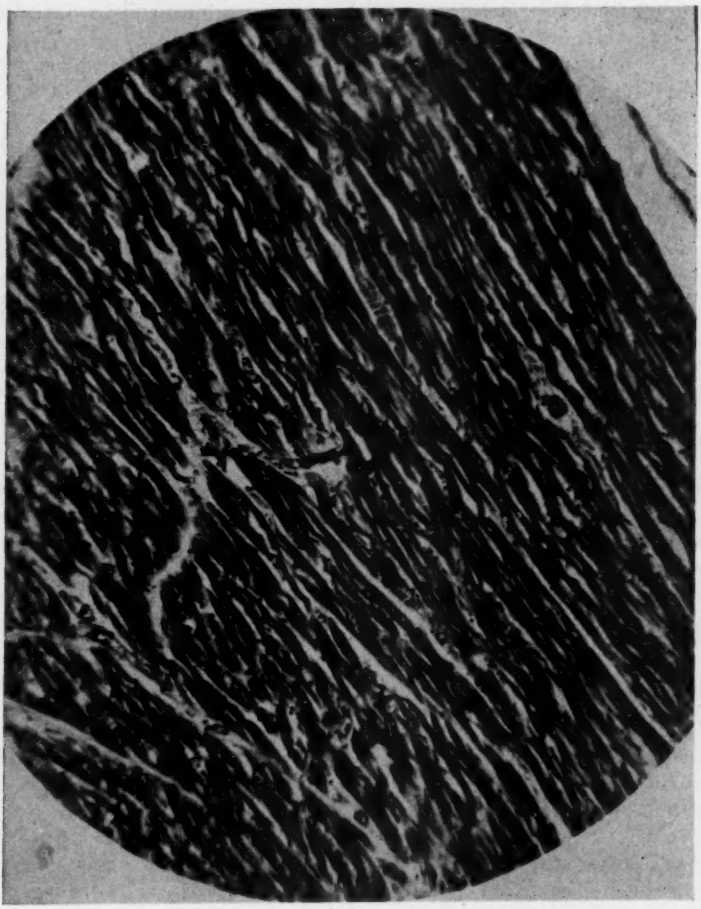

Fig. 2 (Case 42).—Low-power field, showing area of normal myocardium.

mortem examination the kidneys showed chronic and subacute glomerulonephritis. The heart weighed 550 gm. Uremic pericarditis and left ventricular hypertrophy were present. Microscopic examination of the myocardium showed edema and infiltration with chronic inflammatory cells. The condition of the heart was consistent with the changes seen in hypertension and terminal uremia.

SUMMARY

The condition of the heart was evaluated on 109 men who had suffered from beriberi and severe malnutrition during the 44 months they were Japanese prisoners of war. These men, whose ages ranged from 25 to 69, were seen at various times between 1945 and 1951. They were apparently in good health before imprisonment and were treated for beriberi after release from prison. The purpose of the study was to determine whether beriberi, which causes acute myocardial failure, leaves any residual heart disease.

One hundred one of the 109 men, or 92.7%, had no evidence of heart disease from the history, physical examination, roentgenogram for heart size, electrocardiogram, or other studies. Five men had definite heart disease, of whom two had inactive rheumatic heart disease, one had a myocardial infarction, one had arteriosclerotic heart disease, and one had arteriosclerotic and hypertensive heart disease. Three other men had probable arteriosclerotic heart disease. Of the 101 without evidence of heart disease, 3 had hypertension without evidence of heart strain, 2 had generalized arteriosclerosis without heart disease, and 2 had questionable cardiac symptoms which were believed to be on a functional basis. All the cases of cardiovascular disease could be accounted for on the basis of some cause other than beriberi.

One patient died of postinfectious cirrhosis of the liver three years after the onset of hepatitis. During the year before his death there was no evidence of heart disease, but on postmortem examination a patchy fibrosis of the myocardium was observed. It could not be determined whether this was the result of beriberi or secondary to terminal cirrhosis.

In general, the conditions most frequently seen in acute beriberi heart disease, such as edema, enlargement of the heart, low amplitude of the QRS complexes, prolongation of the Q-T interval, and flattening of the T waves were not found. In general, the blood pressures were normal, the heart rates were normal, the hemoglobin levels were normal, and the serum proteins, when determined, were normal.

CONCLUSIONS

Patients with beriberi who survive the acute stages of the disease and who are properly treated do not have residual clinical heart disease from the beriberi.

Among patients who have recovered from beriberi the incidence of cardiovascular disease from other causes is probably no higher than would normally be expected.

It is possible that in some patients subclinical microscopic changes in the myocardium may persist after the beriberi. It is also possible that, as a result of chronic alcoholism or some other continued nutritional deficiency, the acute stages of beriberi heart disease may be protracted or recurrent and heart failure may occur late in the disease. Such patients probably have not been adequately treated and should be considered as having prolonged acute beriberi heart disease rather than residual heart damage.

It did not appear that the 44 months on low-calory, low-fat diets decreased the incidence of arteriosclerosis in these men.

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TOXOPLASMOSIS IN THE HUMAN ADULT

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HUMAN toxoplasmosis has been recognized with increasing frequency since the first description of the disease by Jankû [1] in 1923 and the demonstration by Wolf, Cowen, and Paige [2] of Toxoplasma as a cause of congenital encephalomyelitis with hydrocephalus, intracerebral calcifications, microcephaly, chorioretinitis, and microphthalmos. Most of the cases in the literature have been of infants,[3] and there is an impressive body of evidence that the infection is acquired *in utero* from mothers who present no signs of infection.[4] A few cases of toxoplasmosis occurring in adults have been described. These have differed from the infantile form in that a maculopapular rash and evidence of pneumonitis, acute encephalitis,

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1. Jankû, J.: Pathogenesis and Pathologic Anatomy of Coloboma of the Macula Lutea in an Eye of Normal Dimensions and in a Microphthalmic Eye with Parasites in the Retina, Časop. lék. česk. **62**:1021-1027; 1054-1059; 1081-1085; 1111-1115; 1138-1143, 1923.

2. Wolf, A.; Cowen, D., and Paige, B. H.: Human Toxoplasmosis: Occurrence in Infants as an Encephalomyelitis; Verification by Transmission to Animals, Science **89**:226-227, 1939.

3. Sabin, A. B.: Toxoplasmosis: A Recently Recognized Disease of Human Beings, Adv. Pediat. **1**:1-56, 1942.

4. (*a*) Wolf, A.; Cowen, D., and Paige, B. H.: Fetal Encephalomyelitis: Prenatal Inception of Infantile Toxoplasmosis, Science **93**:548-549, 1941. (*b*) Callahan, W. P.; Russell, W. O., and Smith, M. G.: Human Toxoplasmosis: A Clinicopathologic Study with Presentation of 5 Cases and Review of the Literature, Medicine **25**:343-397, 1946. (*c*) Binkhorst, C. D.: Toxoplasmosis, Leiden, Netherlands, H. E. Stenfert Kroese's Uitgevers-Maatschappij N. V., 1948. (*d*) Eichenwald, H.: Experimental Toxoplasmosis: I. Transmission of the Infection in Utero and Through the Milk of Lactating Female Mice, Am. J. Dis. Child. **76**:307-315 (Sept.) 1948. (*e*) Cowen, D., and Wolf, A.: Experimental Congenital Toxoplasmosis: III. Toxoplasmosis in the Offspring of Mice Infected by the Vaginal Route; Incidence and Manifestations of the Disease, J. Exper. Med. **92**:417-429, 1950. (*f*) Frenkel, J. K., and Friedlander, S.: Toxoplasmosis: Pathology of Neonatal Disease; Pathogenesis, Diagnosis and Treatment, Report 141, Federal Security Agency, United States Public Health Service, 1952.

and myocarditis were prominent in the clinical picture, whereas cerebral calcifications or chorioretinitis have been absent.[5]

The first case considered to be toxoplasmosis in an adult was reported in 1940 by Pinkerton and Weinman.[6] The patient was a 22-year-old Peruvian who died after a brief illness that was complicated by coexistent bartonellosis. The diagnosis was made only after a postmortem examination demonstrated Toxoplasma in sections of most of the abdominal and thoracic viscera and the brain. Proof of the nature of the infecting agent and evidence that the infection had been recently acquired were lacking.

In 1941 Pinkerton and Henderson[7] encountered in St. Louis two more fatal adult cases of an acute, febrile illness characterized by a rickettsiosis-like exanthem and atypical pneumonitis. In the first case Toxoplasma organisms were seen in the lung, heart, and spleen. The tissues from the second patient contained Toxoplasma in the lungs, heart, liver, spleen, and brain. The diagnosis in the second case was supported by isolation of Toxoplasma from guinea pigs that had been given injections of blood drawn shortly before the patient's death and was confirmed at autopsy by the isolation of Toxoplasma in mice which had been given injections of emulsions of the infected human tissues. The demonstration of the organisms in mice is convincing evidence of the disease because mice seldom, if ever, are carriers of Toxoplasma, whereas guinea pigs and certain other animals are known to be naturally subject to the infection.[8] It is noteworthy that in one of these cases in which little or no neurologic disturbance was clinically manifest postmortem examination disclosed a widespread meningoencephalitis. Unfortunately, a detailed description of the lesions in the brain is not available. Again in these cases specific information regarding the time of onset of the disease could not be obtained, but the infection was assumed, from the apparent age of the lesions, to have begun shortly before death. Ticks were suggested as possible vectors.

Nery Guimarães reported another adult case of toxoplasmosis in an 18-year-old Brazilian.[8] Autopsy revealed severe meningoencephalomyelitis, and organisms were seen in the brain, liver, heart, hypophysis, and pancreas. There was no clear evidence of other complicating illness.

Toxoplasmosis has been reported in two additional adults, but a review of the data indicates that the diagnosis in these cases can be accepted only with reservations. In one of these cases,[9] the diagnosis was determined by the finding of Toxoplasma-like organisms in a muscle biopsy specimen, but attempts to establish the identity of the organisms by animal passage gave results that were not characteristic of infection with Toxoplasma. Furthermore, the serum of this patient did not con-

5. Sante, L. R.: Roentgen Manifestations of Adult Toxoplasmosis, Am. J. Roentgenol. **47**:825-829, 1942.

6. Pinkerton, H., and Weinman, D.: Toxoplasma Infection in Man, Arch. Path. **30**:374-392 (July) 1940.

7. Pinkerton, H., and Henderson, R. G.: Adult Toxoplasmosis: A Previously Unrecognized Disease Entity Simulating the Typhus-Spotted Fever Group, J. A. M. A. **116**:807-814 (March 1) 1941.

8. Nery Guimarães, F.: Toxoplasmose humana: Meningoencefalomielite toxoplasmica; ocorrência em adulto e em recemnascido, Mem. Inst. Oswaldo Cruz **38**:257-320, 1943.

9. Syverton, J. T., and Slavin, H. B.: Human Toxoplasmosis, J. A. M. A. **131**:957-959 (July 20) 1946.

tain detectable amounts of antibody, even when examined several years after the acute infection.[10] The other patient [11] had recurrent cutaneous eruptions, chorioretinitis, and eosinophilia. He was found to have antibodies for Toxoplasma and a positive reaction to the skin test, but several attempts to isolate the organism were unsuccessful.

Callahan, Russell, and Smith [4b] mentioned another instance of the disease, a case observed by Randall, in which toxoplasmosis was diagnosed from the histologic material and was characterized by destruction of bone, splenic enlargement, and encephalomalacia. The patient was an American soldier who died after an illness of five months. A detailed study of this case has not yet been reported.

Sabin reported two instances of toxoplasmosis in children in whom the infection was apparently acquired after birth.[12] However, the most convincing proof by serologic methods that toxoplasmosis may be acquired during adult life and that such as an infection need not be fatal was offered by Ström.[13] He recounted two cases in which the infection had developed in laboratory technicians working with the organism. Both patients had no antibody initially but subsequently were found to have diagnostic titers. One patient had a maculopapular rash and evidence of myocarditis and meningitis. In the other a brief febrile illness was accompanied with cervical adenopathy. Another recent fatal case in a laboratory worker in Memphis, Tenn., has been brought to our notice.[14] The illness was acute and of short duration, and the principal features of it were a maculopapular eruption and delirium. Serologic confirmation of the diagnosis was obtained, but only a limited autopsy was permitted.

The extreme rarity of active toxoplasmosis in adults is in striking contrast to the apparently widespread occurrence of the parasite of this disease throughout the animal kingdom in all parts of the world. Toxoplasma has been demonstrated in a wide variety of domestic and wild animals and birds.[4b] The identification has been by morphologic means alone in most instances, but the evidence for its occurrence in many domestic animals and pigeons is probably secure and reliable, for rigorous methods which exclude the many other organisms that resemble Toxoplasma morphologically have been employed.[15] Moreover, it has been determined in all population groups studied thus far that antibodies and skin sensitivity to Toxoplasma rise with increasing age, thus indicating continued acquisition of inapparent toxoplasmosis in the adult population.[16] The data suggest that toxoplasmosis is a rather frequent disease in adults but that the inconspicuous symptoms rarely permit clinical diagnosis.

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10. Feldman, H. A.: Unpublished observation.

11. Brennan, A. J.; Brown, T. M.; Warren, J., and Vranian, G.: A Syndrome Characterized by Generalized Cutaneous Eruption, Chorioretinitis and Eosinophilia Probably Due to Chronic Toxoplasma Infection, Am. J. Med. **7**:431-436, 1949.

12. Sabin, A. B.: Toxoplasmic Encephalitis in Children, J. A. M. A. **116**:801-807 (March 1) 1941.

13. Ström, J.: Toxoplasmosis Due to Laboratory Infection in 2 Adults, Acta med. scandinav. **139**:244-252, 1951.

14. Sexton, R.; Eyles, D. E., and Dillman, R. E.: Personal communication to the authors.

15. Sabin.[8] Feldman.[10] Sabin, A. B.: Symposium: Toxoplasmosis: Diagnosis and Treatment, Tr. Am. Acad. Ophth. **54**:190-206, 1950.

16. Feldman, H. A., and Sabin, A. B.: Skin Reactions to Toxoplasmic Antigen in People of Different Ages Without Known History of Infection, Pediatrics **4**:798-804, 1949.

The case of toxoplasmosis in a human adult which is the subject of this communication is particularly noteworthy because of the following features: 1. The diagnosis was suggested by the histologic examination of a muscle biopsy specimen. 2. Toxoplasma organisms were isolated from a muscle biopsy specimen. 3. The diagnosis was made in sufficient time to institute intensive therapy with several agents that have proved effective in experimental animals. 4. Serial antibody determinations indicate that this was a recently acquired infection. 5. A complete postmortem examination was done with the demonstration of disseminated polymyositis and meningoencephalomyelitis. 6. The organisms were isolated from many organs.

REPORT OF CASE

History.—G. B. (BCH 1372852), a 60-year-old white woman, entered the Boston City Hospital on Sept. 14, 1950, because of pain in the knees, hips, and back and a generalized skin rash. She stated that she had been entirely well and working regularly as a housekeeper until 10 to 12 days before entry, when she noted the progressive development of malaise and excessive fatigability. About nine days before entry she had begun to have dull, aching pains in both knees, both hips, and the upper dorsal and cervical vertebral areas. The pains were not associated with redness, tenderness, or swelling, and they persisted for four or five days with little or no fluctuation in intensity. The pains ceased coincidentally with the appearance of a rash which, from the description, consisted of red, nonpruritic macules 1 cm. or less in diameter, visible first on the anterior thoracic surface and then extending to the flexor surfaces of both arms. By the third day after its initial appearance the rash had spread over the chest, arms, anterior surfaces of the lower extremities, and the face near the external canthus of the eyes and lateral to the alae nasi. The palms, soles, and lower abdomen were not involved, and the patient did not know whether the back had been affected. The skin lesions were never vesicular and tended to fade after two or three days. During this period the patient had felt mildly feverish. Her appetite had remained good until three or four days before entry, when her anorexia became so severe that she accepted only fluids. During the preceding two or three days a mild, persistent, nonproductive cough was noted, and shortly before entry the urine was observed to be dark in color. At no time were there headache, nausea, vomiting, diarrhea, visual disturbances, or other pulmonary, cardiac, or gastrointestinal symptoms. A loss of 10 to 20 lb. (4.5 to 9.1 kg.) in weight was said to have occurred since the onset of the illness.

The past history contributed no positive data. The patient had been pregnant three times and was delivered of three normal children, all of whom are now apparently healthy adults. One of her daughters gave birth to two healthy children. No recent exposure to infectious diseases was known, and tick or other insect bites were denied. Recent contact with rodents, pigeons, parrots, parakeets, cats, or dogs was not recalled. Pork had not been eaten during the preceding two or three weeks. The only medicaments that she had received were aspirin and chloramphenicol, the latter for two days preceding admission to the hospital. There had been one brief exposure to dry-cleaning fluid, but contact with other chemical agents was not known. The family and social histories were otherwise not remarkable.

Results of Examination.—On admission the temperature was 104.6 F., the pulse rate, 118, the respiration rate, 28, and the blood pressure, 156/90. The patient appeared to be well nourished and weighed about 140 lb. (63.5 kg.), but there was evidence of recent loss of weight. She was alert and rational. A fading brown macular rash was seen over the trunk and extremities but spared the scalp, back, lower abdomen, palms, and soles. The conjunctivae and sclerae were clean, and the eyes were otherwise normal. Repeated examination of the fundi during the course of the illness failed to reveal any abnormalities except constant though minimal changes in the caliber of the retinal arterioles. The teeth were carious; the right tonsil was slightly injected, and several small discrete nontender lymph nodes were felt in the posterior cervical region. The heart, lungs, abdomen, pelvis, and rectum were all within normal limits, and examination of the nervous system disclosed no abnormalities. There was no icterus, and the liver was not tender to percussion. No cardiac murmurs were heard. The spleen was not palpable.

Laboratory Data.—During the first day in the hospital, the hemoglobin concentration was 12 gm. per 100 ml. of blood and the white blood cell count was 7,440 per cubic millimeter. There were 68% neutrophiles (1% nonsegmented), 19% lymphocytes (3% large lymphocytes), 8% atypical lymphocytes, 3% eosinophiles, and 2% metamyelocytes. The erythrocytes and thrombocytes (platelets) were normal in appearance. The urine had a specific gravity of 1.024 and a pH of 5.5 and contained neither albumin nor sugar. Traces of acetone were present on the initial examination but disappeared on the following day. The urinary sediment contained an occasional leucocyte and rare coarse granular casts. Seventeen blood cultures, including four done anaerobically, two cultures of the bone marrow, four of the stool, four of the throat, and seven of the urine, yielded no pathogenic organisms. Agglutination tests for typhoid, paratyphoid, Brucella, and Shigella organisms gave negative results at the time of entry and again one month later. Complement-fixation studies for murine and epidemic typhus, Rocky Mountain spotted fever, and rickettsialpox likewise gave negative results, as did serial tests for heterophile antibodies. The blood urea nitrogen was 13 mg. per 100 ml., and this level did not change significantly during the entire hospital course. The reaction to the Hinton test on the blood was negative. The tuberculin reaction was positive in 1:1,000 dilution. No acid-fast bacilli were found in two

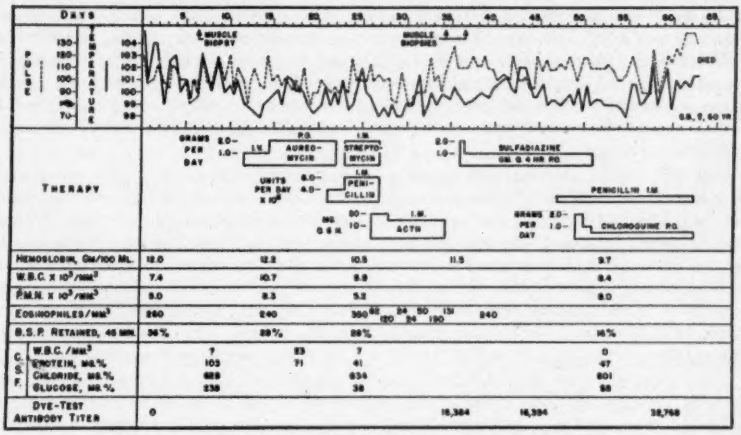

Fig. 1.—Course of adult patient with toxoplasmosis.

sputums, and one sample of gastric contents failed to produce tuberculosis when injected into a guinea pig. The first tests of hepatic function showed evidence of slight disturbance of function: The sulfobromophthalein (bromsulphalein®; B. S. P.) sodium retention at 45 minutes was 36%; cephalin flocculation and zinc flocculation were normal. The thymol turbidity was 8.7 units; prothrombin time, 84%; icteric index, 8.5; albumin-globulin ratio, 3.5/2.2, and the alkaline phosphatase, 2.43 units (Bodansky); urinary urobilinogen was detected in 1/40 dilution. Reactions to tests of the urine for bile were negative. Repeated examinations of the stool disclosed a 1+ reaction to the guaiac test on only one occasion.

Initial roentgenographic studies of the chest revealed minimal cardiac enlargement but no evidence of pneumonitis. A survey of the osseous system at entry and about 45 days later showed no abnormalities in the skull, chest, pelvis, vertebrae, or long bones, save for minimal hypertrophic arthritis and mild osteoporosis of the vertebrae and pelvis. Examination of the gall bladder suggested the presence of nonopaque calculi.

Course in the Hospital.—The course, therapy, and some of the more pertinent laboratory data are summarized in Figure 1. The patient was in the hospital for 60 days. During the first week she remained febrile but was mentally clear. Her temperature fluctuated between 99 and 104 F., with daily spiking temperature elevations unaccompanied with chill. The pulse rate

remained elevated, and the respiratory rate and blood pressure did not change. There were no special complaints. By the end of the first week the rash had disappeared. The urine and blood were not significantly changed.

A biopsy specimen of the right gastrocnemius muscle, taken on the seventh day, was reported as showing scattered focal infiltrations of lymphocytes, plasma cells, and mononuclear cells with degeneration of isolated muscle fibers. This was interpreted as being consistent with a nonspecific disseminated polymyositis or an interstitial myositis. The total eosinophile count of the blood at this time was 260. Smears of the bone marrow were not remarkable.

During the second week the patient manifested increasing anorexia but complained of no pain or other distress. The physical findings were unchanged. The sulfobromophthalein retention was 28%; serum chlorides were 88 mEq., and the carbon-dioxide-combining-power was 23 mEq. An electrocardiogram on the 11th day was normal except for sinus tachycardia. On the 12th hospital day the patient became drowsy, stuporous, and slightly cyanotic. Her skin was cold and clammy, and blood pressure was unobtainable. A lumbar puncture at this time was apparently traumatic (bloody tap); the pressure was unobtainable, and cerebrospinal fluid contained 300,000 erythrocytes and 200 leucocytes and 102 mg. of protein, 238 mg. of sugar (the tap was performed during the intravenous administration of dextrose solution), and 628 mg. of chlorides, per 100 ml. A culture was negative for pathogens and the Hinton reaction was negative. The colloidal gold curve was 1223333210. After the administration of dextrose, saline solution, and 500 ml. of whole blood, the blood pressure rose to 130/100, and the patient became more responsive but remained confused. Results of a physical examination were otherwise noncontributory, except for the presence of a gallop rhythm. The reaction to a Rumpel-Leede test was negative, and the bleeding time (Duke method) was within normal limits. Multiple cultures were all negative for pathogenic organisms.

Beginning on the 13th day, aureomycin was administered in doses of 0.5 gm. intravenously every 12 hours in 1,500 ml. of fluid, and for a few days afterward the patient's condition seemed improved. On the 15th day it was necessary to give the aureomycin orally in a dose of 0.5 gm. every six hours because of the poor condition of the patient's veins. The patient tolerated this well and continued to show progressive decrease in the confusion and anorexia. On the 16th day, petechial hemorrhages appeared over the skin of the anterior abdominal wall, flanks, and upper arms. New lesions appeared during the next 48 hours but were never present in the nail beds, retinae, or conjunctivae. Multiple aerobic and anaerobic cultures of the blood and bone marrow were negative at this time, as was the result of a gonococcal complement-fixation test.

The patient was then given 4,000,000 units of penicillin per day in divided doses, and when her fever persisted this was increased to 8,000,000 units with 2 gm. of streptomycin per day added, but there was no significant clinical response and the spiking temperature elevations continued. By the 21st hospital day the patient was confused and at times frankly delirious. She was disoriented as to time and place, was unable to recognize her family, and misidentified the physicians and nurses who were caring for her. She was alternately garrulous and sullen or querulous. Her speech was well articulated, and no aphasic disturbance was noted. There were no abnormalities of cranial nerves. A coarse tremor of the hands was noted. The neck was supple; the arms and legs were strong; the movements were fairly well coordinated, and the tendon reflexes were about equal on the two sides. The left plantar reflex was equivocal and the right one definitely flexor. Crude tests of sensation gave normal results. The cerebrospinal fluid was xanthochromic at this time and contained 300 erythrocytes and 23 leucocytes (20 lymphocytes and 3 neutrophiles) per cubic millimeter; the total protein was 71 mg. and the colloidal gold curve 2233333210. Cultures were negative. By the 23d day the patient had become stuporous, and the general impression was that she had suffered diffuse cerebral damage. At this time, the albumin-globulin ratio was 1.8/2.5, the prothrombin time was 30%, and the sulfobromophthalein retention was 28%.

The patient's condition continued to deteriorate, and on the assumption that she might be suffering from one of the "collagen diseases" corticotropin (ACTH) was given in doses of 20 mg. every six hours for two days, followed by the same dose every eight hours for six more days. Control eosinophile counts ranged between 240 and 350 cells per cubic millimeter, and there was a prompt response to the hormone treatment, with eosinophile counts remaining at less than half the initial levels until the last two days of therapy (Fig. 1). The fever was reduced during

this period, but the temperature was never normal. There was no striking change in the patient's clinical appearance or in physical findings except that the tremor disappeared.

Another muscle biopsy specimen, this one from the left gastrocnemius muscle, was obtained on the 35th hospital day, and in addition to the focal inflammatory reaction Toxoplasma organisms were seen in the muscle fibers.[17] A review of the previous muscle biopsy specimen revealed Toxoplasma organisms to be present there as well. At this time the hemoglobin concentration was 11.5 gm.; the fasting blood sugar, 144 mg. per 100 ml., and the carbon-dioxide-combining power, 24 mEq.; chlorides were 93 mEq., and the albumin-globulin ratio was 2.4/3.5. Sulfadiazine was then given in full doses, and the blood level was maintained between 10 and 15 mg. per 100 ml. for two weeks. The clinical course of the disease was not altered. The cerebrospinal fluid at the end of the course of sulfadiazine therapy contained no cells, and cultures were again negative, but there was 47 mg. of protein, as well as 58 mg. of sugar and 601 mg. of chlorides, per 100 ml. The colloidal gold curve was 5554433221. An electrocardiogram showed prolongation of the Q-T interval, but this became normal within two weeks.

By the 50th hospital day the patient's condition was deteriorating rapidly. Studies of her liver function showed persistent evidence of hepatic dysfunction, with sulfobromophthalein retention of 16%, cephalin flocculation, 3+, zinc flocculation, 1+, thymol turbidity, 16.1 units, alkaline phosphatase, 2.95 units, prothrombin time, 73%, albumin-globulin ratio, 2.5/2.4, and normal icteric index. The blood calcium was 6.8 mg. per 100 ml. on two occasions, and phosphorus was 2.4 and 2.1 mg. per 100 ml. on two determinations. The urinary Sulkowitch test gave a 1+ reaction. An electroencephalogram was interpreted by Dr. Wesley Watson as showing bilaterally synchronous spike-and-slow-wave forms consistent with a diffuse disorder of cerebral function, possibly arising in the diencephalic region.

It was then decided in desperation to try one of the antimalarial drugs, and chloroquine was selected. The dosage was 2 gm. the first day, 1 mg. the second, and 0.5 gm. daily thereafter for 11 days. Some slight improvement in the mental status occurred in the first few days, but this was followed by relapse and death on the 62d hospital day. Terminally, coarse inspiratory rales were heard throughout the left lung. There were still no lateralizing neurological signs, other than an extensor plantar reflex on the left side. No definite motor or sensory abnormalities were found at any time, nor were any changes noted in the function of the cranial nerves. The skeletal muscles were soft, flabby, and slightly tender.

Postmortem Observations (Mallory Institute of Pathology, No. 50:854).—Gross Examination: An autopsy was performed 12 hours after death. The body was emaciated. No discoloration or pigmentation was noted except for livor over the left side of the forehead and lower abdomen. Initial exploration of the viscera was carried out aseptically, and random samples of heart, lungs, liver, spleen, kidney, and psoas muscle were excised and placed in sterile containers for animal inoculation. Sections of cerebral cortex and medulla were also excised and 10-ml. samples of blood and of cerebrospinal fluid were obtained aseptically.

Gross examination of the thoracic and abdominal organs revealed no abnormalities. The liver weighed 900 gm. but was otherwise not remarkable in color, consistency, or architecture. Significant gross changes were limited to the brain.

There were no surface abnormalities of the brain except for slight atrophy of the frontal convolutions. The leptomeninges were neither thickened nor opaque, and the large arteries were relatively free of atherosclerosis. On frontal sections of the cerebrum and horizontal sections of the brain stem, four lesions were seen. One of these was in the middle portion of the left putamen (Fig. 2*A*); a second was in the right precentral convolution near the arm area of the motor cortex. The third lesion was located in the white matter of the right frontal lobe, and the fourth was in the cortex and the subcortical white matter of the left occipital lobe (one of the lateral convolutions). These lesions were all roughly circular and ranged from 0.8 to 1.4 cm. in diameter. The central parts were soft and varied from pale green to tan, and the margins were slightly hemorrhagic. There was no distortion of the brain tissue in the vicinity of these lesions. The ventricles were of average size, and the ependymal surfaces were smooth.

The spinal cord was of natural appearance, and the arachnoidal membrane was thin and relatively transparent. The spinal roots were of average size. No gross lesions were seen in multiple transverse sections.

17. Dr. Q. M. Geiman assisted in identifying the organism.

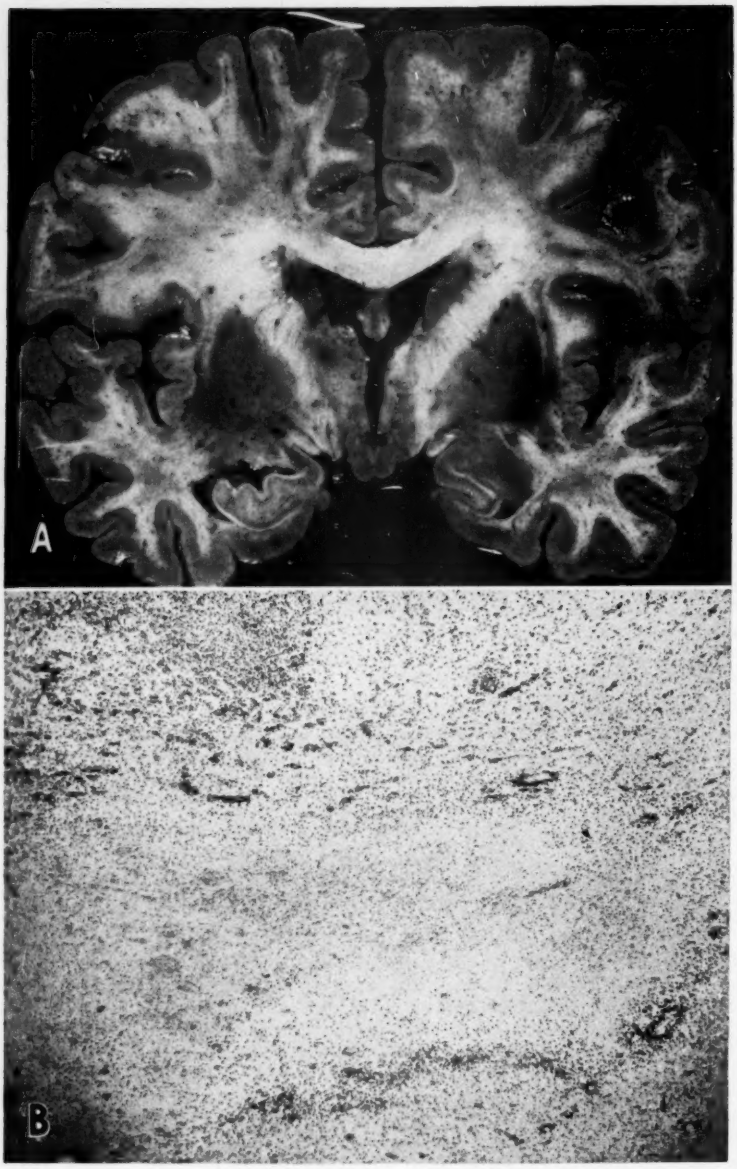

Fig. 2.—*A*, brain, coronal section: Oval-shaped zone of necrosis in left putamen. *B*, brain: Low-power view of cerebral lesions. Widespread necrosis of tissue in center of field and focus of necrosis with macrophagic infiltration in upper left. Hematoxylin and eosin stain.

Microscopic Examination: Tissues for histologic examination were preserved in Zenker's fixative (solution of corrosive mercuric chloride, potassium bichromate, sodium sulfate, and water) and in 10% neutral formalin® solution. For general histologic study Giemsa's stain, ploxine methylene blue, hematoxylin and eosin, hematoxylin and van Gieson's stain, and Mallory phosphotungstic acid and hematoxylin were employed. For specific studies the following stains were used: Turnbull's blue (ferrous ferricyanide) for iron with basic fuchsin counterstain, Ziehl-Neelsen stain for ceroid pigment, Foot's modification of the Bielschowsky reticulum stain, the Loyez stain for myelin sheaths, the Gross-Bielschowsky method for axis cylinders, Sudan III and hematoxylin for fat, Penfield's combined method for microglia and oligodendroglia, and Cajal's gold chloride sublimate stain for astrocytes.

Scattered throughout the myocardium were relatively large numbers of pseudocysts of Toxoplasma. As many as five such structures per high-dry field could be seen. These occurred generally within the muscle fiber as large spindle-shaped clusters of minute basophilic nuclear masses. Mutiple blocks were examined from the region of the conduction system, and numerous subendocardial fibers were seen to be involved, though typical Purkinje fibers could not be identified. Parasitized muscle fibers were strikingly free of inflammatory reactions. There were, however, a few small foci of infiltrations with histiocytes and lymphocytes accompanied with occasional plasma cells, mast cells, and pyknotic neutrophilic leucocytes. No fibroglial fibers could be demonstrated in the vicinity of these lesions. There was apparent loss of myocardial fibers focally, and occasional fragments of sarcoplasm could be seen. Many of the macrophages contained granular, yellow, fuchsinophilic pigment that failed to stain with iron or acid-fast stains. No pseudocysts were seen within inflammatory foci, and free-lying organisms could not be found. Occasional minute foci of acellular collagen were observed throughout, though these were unrelated to the inflammatory foci or the presence of pseudocysts.

The pseudocysts varied from 5 to 35 μ in diameter and up to 100 μ in length. Occasionally the larger pseudocysts distended the parasitized muscle fibers, but the smaller ones were seen usually within an undistended muscle fiber, surrounded by a thin limiting membrane suggesting a capsular structure. Within the pseudocysts the individual organisms were seen only as clusters of nuclei that remained discrete from one another, although they were closely packed. Ruptured pseudocysts were seen, apparently as a mechanical artifact in view of the absence of local inflammation (Fig. 4*B*), and in these the nuclei were surrounded by small crescent-shaped masses of pale basophilic cytoplasm, averaging 3.1 μ in length and 1.2 μ in diameter. The organisms were asymmetric, one end being sharper than the other. The nuclei were eccentrically located at the blunter end of the organism, and at this point the nucleus appeared to fill the cell, so that edges of nuclei and the cell membrane coincided without a visible rim of cytoplasm. With routine stains the nuclei appeared as spherical or slightly ovoid basophilic masses. The chromatin was either homogeneous or somewhat reticulated. Nuclear borders were generally rather poorly delineated. In Zenker-fixed material, the nuclei averaged 0.8 μ in diameter. With reticulum stains, however, sharper definition was apparent and the nuclear diameters measured 1.1 μ.

The lungs were congested and slightly edematous, with scattered areas of bronchopneumonia and only minimal interstitial infiltration. No Toxoplasma organisms were seen. There was focal congestion of the spleen. The pancreas showed minimal interstitial infiltration by mononuclear cells, slight focal fat necrosis, and fibrosis.

In the liver no parenchymal necroses or active inflammatory changes were seen. There was a slight, uniform increase in acellular periportal collagen, and the central liver cord cells contained increased amounts of granular, yellow-green pigment that failed to stain with iron, acid-fast, or fuchsin stains. The Kupffer cells contained small amounts of yellowish pigment which gave a positive stain for iron. The central sinusoids were congested and the parenchymal cells atrophic, with minimal fatty vacuolation of midzonal cells.

The adrenal cortices contained only a small number of lipid vacuoles, and the glands were otherwise not remarkable. A rare renal collecting tubule contained granular greenish pigment, negative to iron stain, but the kidneys were otherwise not unusual. The uterus, ovaries, and anterior lobe of the hypophysis were not remarkable, nor were multiple sections of the gastrointestinal tract, taken at various levels. Bone marrow obtained from several sites showed some generalized hypocellularity but was otherwise not unusual. Several sections of skin chosen at random from chest and abdomen revealed a thin epidermis with scattered lymphocytes,

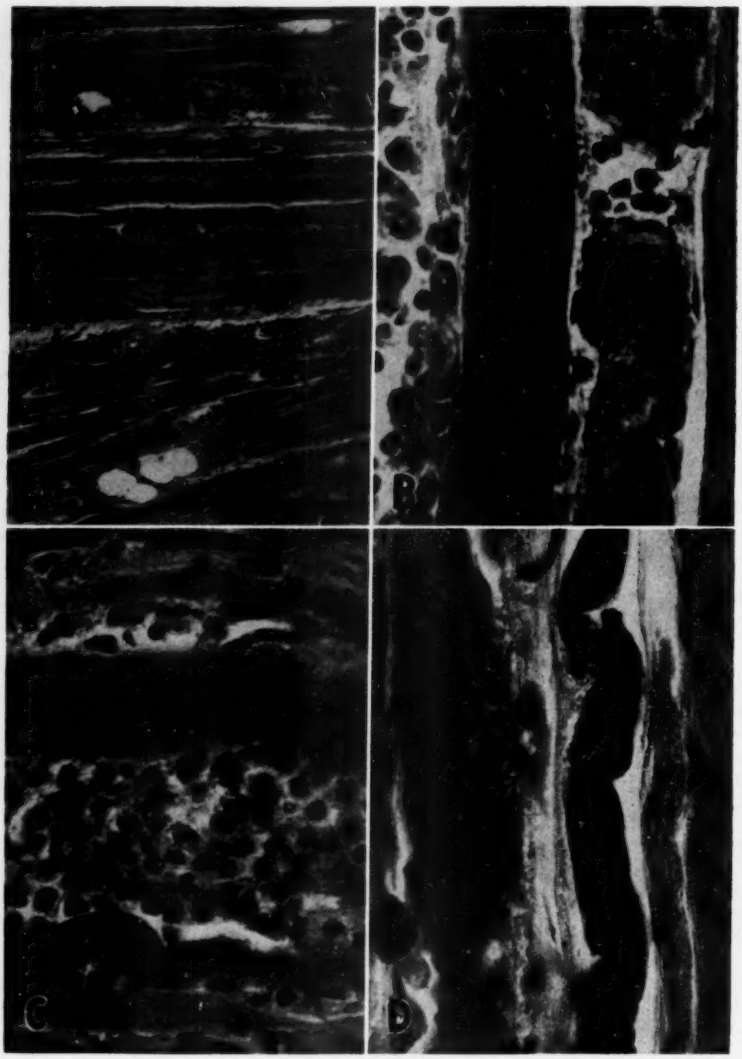

Fig. 3.—*A*, left biceps: Degeneration of muscle fibers and scattered cellular infiltrations (× 100). *B*, left biceps: Two muscle fibers in different stages of degeneration. On right sarcoplasm is disintegrated, with histiocytic infiltration. On left sarcoplasm is replaced by macrophages, leucocytes, and plasma cells (× 800). *C*, left biceps: Degeneration of muscle fiber in center of field with invasion by neutrophilic leucocytes (× 800). *D*, left biceps: Atrophic fibers with basophilic sarcoplasm and proliferation of sarcolemmal nuclei (× 800). Phloxine-methylene-blue stain.

macrophages, and mast cells in the dermis. No Toxoplasma organisms were seen in sections of the lungs, spleen, pancreas, liver, adrenal glands, kidneys, hypophysis, pelvic viscera, bone marrow, or skin.

Striated muscles: A large number of muscles (lingual, pharyngeal, temporal, sternomastoid, deltoid, pectoral, biceps, triceps, brachioradialis, intercostal, erector spinae, psoas major, diaphragm, gluteus maximus, biceps femoris, quadriceps, and gastrocnemius) were examined microscopically. Destruction of muscle fibers, infiltrations of inflammatory cells, Toxoplasma pseudocysts, and regeneration of muscle fibers were present in varying degrees in all these muscles (Fig. 3). An average of 1 of every 10 or 12 muscle fibers was in the process of degeneration. Usually only one part of the fiber, an extent equal to 20 to 40 sarcomeres, was involved. The sarcous content of the fiber was swollen, hyalinized, and usually eosinophilic. In most instances the sarcous substance was fragmented. The sarcolemma was interrupted, and some of the sarcolemmal nuclei were shrunken and pale, as though necrotic. Many of the damaged fibers were invaded by mononuclear cells, probably histiocytes, that occasionally assumed the form of fully developed macrophages. Cellular infiltrations tended to occur in the immediate vicinity of the damaged fibers and also in the perimysium around small blood vessels. The predominant cells were lymphocytes, plasma cells, transitional forms of histiocytes, and a few neutrophilic leucocytes and mast cells. These cells formed aggregates inside of which pseudocysts were sometimes seen. More usually, however, the parasites were observed within apparently unaffected muscle fibers or were lying freely in the endomysium between fibers. Discrete Toxoplasma organisms could be identified in only two of the inflammatory foci. In addition to the normal and disintegrating muscle fibers, there were others that were conspicuous because of their small diameter, poor striations, and basophilia. In these fibers the sarcolemmal nuclei were large and hyperchromatic, with prominent nuclei, were increased in number, and sometimes occupied the central region of the muscle fiber. These were evidently proliferating sarcolemmal nuclei. The parts of the muscle fiber at either end of the degenerated segment often exhibited such changes. Damage to blood vessels or supporting tissues of the muscle could not be demonstrated. Even in the larger inflammatory foci there was little or no fibrin deposited and no visible reaction of the fibroblasts. Swelling of endothelial cells and cellular infiltration of the adventitia were noted in some of the small blood vessels. The muscle spindles did not appear to be involved.

The gastrocnemius muscle was affected more severely than any other striated muscle. In places as many as one-half of its fibers were destroyed. In other muscles the ratio of unaffected to diseased fibers ranged from 10:1 to 5:1. Only three or four damaged fibers were observed in the diaphragm. Although no destruction of muscle fibers was seen in the tongue and pharynx, pseudocysts were noted in both.

Smears were made from carefully macerated striated muscle, and several free-lying pseudocysts with distinct capsules were observed (Fig. 4*A*). At the suggestion of Dr. J. K. Frenkel,[18] reticulum stains were used to stain the capsule, and its argyrophilic nature was demonstrated. as shown in Figure 4*A*.

Blocks of peripheral nerve, spinal ganglia, several blocks of spinal cord and spinal roots, medulla, pons, midbrain, cerebellum, thalamus, lenticular and caudate nuclei, and cerebral cortex and white matter from each lobe of the cerebrum were examined microscopically (Figs. 2, 5. and 6).

Innumerable lesions were seen in all sections of the brain and spinal cord. These were of two types: small clusters of mononuclear cells and large necrotic foci such as had been seen upon macroscopic examination. The small clusters of cells ranged from 0.1 to 1.0 mm. in diameter. They were irregular in shape and were composed of pleomorphic mononuclear cells, probably microgliocytes predominantly. The nuclei were small and polymorphous, stained darkly with hematoxylin, and exhibited very little cytoplasm in any of the routine cell stains. The cells were closely packed in the central parts of the lesion and tended to be more scattered at the periphery. A few cells, probably lymphocytes, plasma cells, or unidentified cells, with small round, darkly staining nuclei were scattered through the lesion. Many of these lesions surrounded or were

18. Dr. Frenkel permitted us to examine some of his histologic material and his preliminary manuscripts.

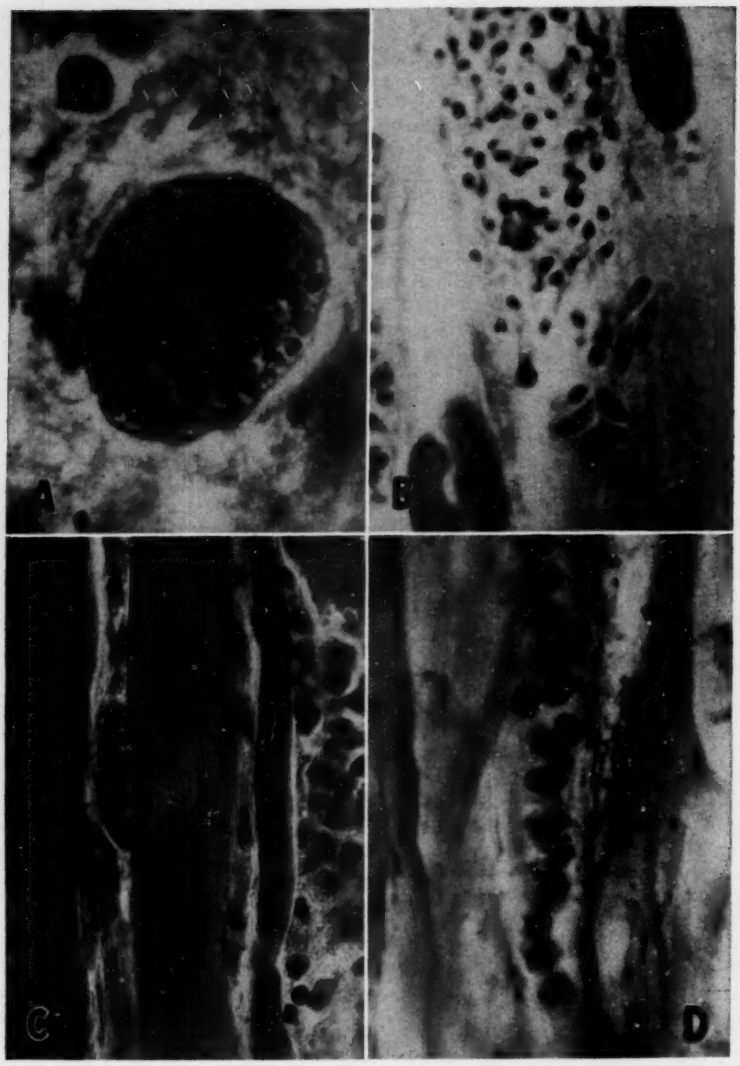

Fig. 4.—*A*, cerebral cortex: Reticulum stain showing well-encapsulated pseudocyst with no surrounding inflammation (× 2,400). *B*, right deltoid: Giemsa stain of muscle fiber. Pseudocyst has ruptured and typical crescentic form of liberated organism can be seen (× 2,400). *C*, left biceps: Pseudocyst on surface of muscle fiber, lying just beneath true sarcolemma. Phloxine-methylene-blue stain; × 800. *D*, smooth muscle of intestinal wall of hamster: Spindle-shaped accumulation of organisms without formation of a pseudocyst. Phloxine-methylene-blue stain; × 2,400.

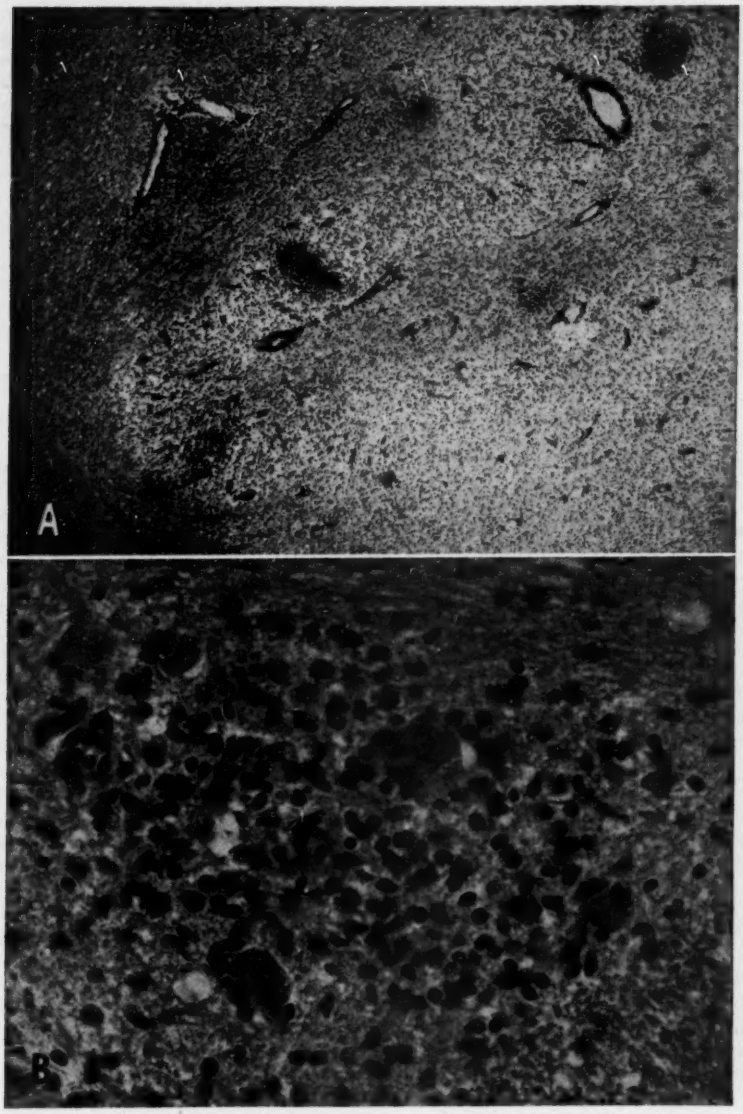

Fig. 5.—*A*, brain: Low-power view of dentate nucleus, illustrating perivascular infiltrations of inflammatory cells and small foci of necrosis of tissue with clusters of histiocytes and transitional microglial cells. *B*, pons: High-power view of clusters of mononuclear cells. Note intact nerve cells. Hematoxylin and eosin stain.

adjacent to small blood vessels in which slight alterations, such as enlargement and slight increase in the number of endothelial cells and infiltration of the Virchow-Robin space in the adventitia by lymphocytes and plasma cells, were noted. In the gray matter degenerating nerve cells were occasionally seen within these lesions, but surviving nerve cells were equally frequent. Medullated nerve fibers and axis cylinders were destroyed in the central parts of the lesions. Around some of these cell clusters or in their margins, there was an increase in the number and size of the astrocytes. Small cysts filled with Toxoplasma organisms were seen in some of the cellular foci, and in a few of them free Toxoplasma organisms could be identified. The veins and other small blood vessels near these cell clusters were surrounded by collars of lymphocytes, plasma cells, and mononuclear histiocytes. A few of the lesions were subpial but were not in relation to any particular process in the meninges. These cell clusters were definitely more numerous in the gray than in the white matter. In the spinal cord only four or five such foci were seen in each section. In the medulla and pons they were more numerous. In the midbrain several of them had become confluent, forming two foci at the medial border of each substantia nigra. Here 20 to 30 pseudocysts could be found within the confines of a single lesion. The dentate nuclei and the thalamus were also quite severely involved. Scattered lesions were seen in all parts of the cerebellar and cerebral cortex and white matter. Usually there were 20 to 25 such foci in a large section, e. g., of a size sufficient to include the whole sagittal diameter of the cerebellum or the coronal diameter of the thalamus.

The larger foci (Fig. 2*B*) ranged from 0.2 to 1.4 cm. and were also of variable shape. The central parts had undergone complete necrosis, and only nuclear debris or the faint outlines of unstained cells and blood vessels remained. In some it was possible to see that the necrotic cells were closely packed macrophages. The borders of such lesions varied. Some were cellular with a mixture of lymphocytes, plasma cells, and histiocytes and the hyperplastic endothelial and adventitial cells of small blood vessels. The perivascular spaces of the small vessels surrounding the necrotic foci were infiltrated with lymphocytes, plasma cells, and mononuclear leucocytes. The borders of other lesions were only sparsely cellular. Plump astrocytes or enlarged astrocyte nuclei were seen around many such lesions. Granular material was present all through these lesions, making it impossible for us to decide whether free Toxoplasma organisms occurred here. A few scattered foci 0.2 to 0.4 cm. in size were filled with fatty macrophages that surrounded surviving small blood vessels, the walls of which were exceedingly cellular owing to the many perivascular lymphocytes and plasma cells and to infiltration of the intervening tissue by similar cells. Many Toxoplasma pseudocysts were seen in two such lesions.

Both the small cell clusters and the larger necrotic lesions were of variable age, as judged by the degree of preservation of the cells in the central parts, the number of cells in the margins, the degree of phagocytic activity in the histiocytes, and the number of fibrous astrocytes in the adjacent tissue. Most of the lesions were several weeks old, and others, very few in number, were only a few days old. The earliest lesion consisted of a small focus in which the tissue was eosinophilic and infiltrated with only a few pleomorphic adventitial histiocytes or microgliocytes. A few Toxoplasma organisms were seen within it.

The pia-arachnoid and the subarachnoid spaces were moderately cellular in some places and not in others (Fig. 6*B*). This focalization of the meningeal infiltrates was noted over the cerebral hemispheres, as well as the brain stem, cerebellum, and spinal cord. The infiltrating cells were lymphocytic and mononuclear with a few plasma cells and rare neutrophilic leucocytes and mast cells. No Toxoplasma organisms were seen in the meninges. Ependymal lesions were not observed in random sections of the walls of the fourth ventricle, aqueduct of Sylvius, and third and lateral ventricles. The only change seen in the choroid plexuses was a slight infiltration of lymphocytes and plasma cells between the epithelium and the endothelial cells in a few places.

Pseudocysts of Toxoplasma in the nervous system had much the same appearance as those in the heart and skeletal muscle (Fig. 4*A, C*). Pseudocysts were observed in places where there was no tissue reaction; free Toxoplasma organisms were rarely seen in the lesions; in fact, free Toxoplasma organisms were identified with certainty in only three of the lesions of the brain, but many may have been overlooked because of the granular debris and precipitated stain from which they could be distinguished only with difficulty. There were many cysts in and around some of the cellular foci.

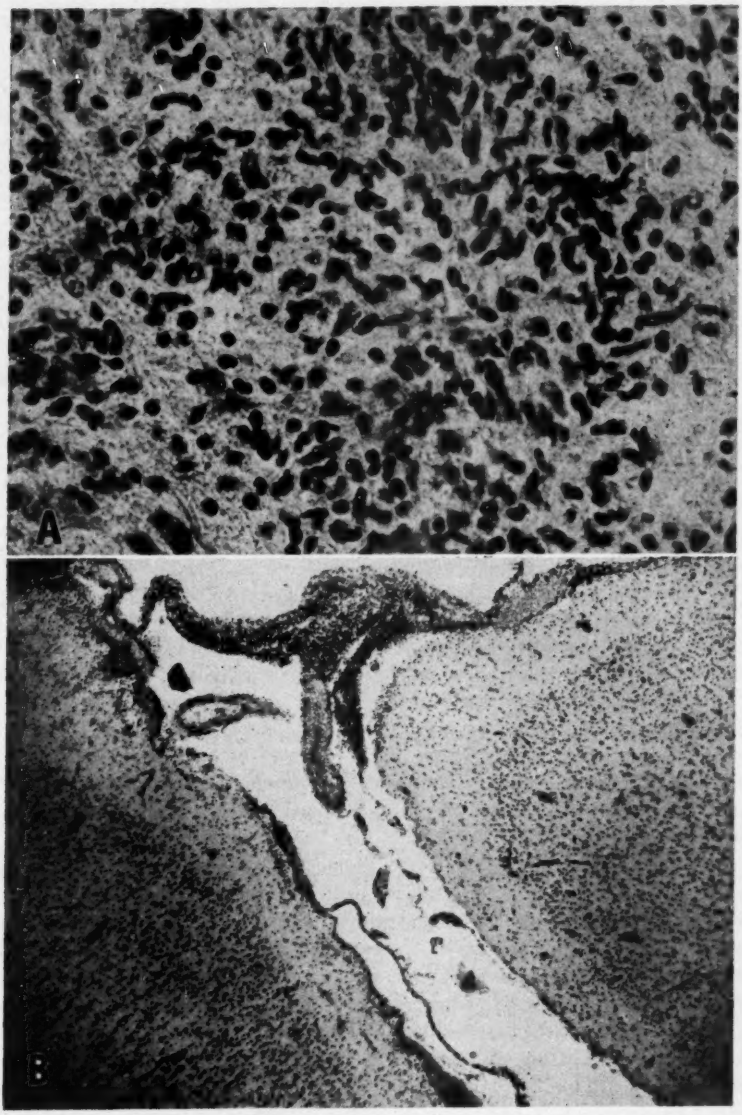

Fig. 6.—*A*, pons: Cluster of mononuclear cells with radial orientation suggesting formation of granuloma. *B*, meninges: Low-power view of cerebral meninges demonstrating infiltration with inflammatory cells. Hematoxylin and eosin stain.

No lesions were found in one retina, but the section contained only the central part of it, between the fovea and the optic disk. In the optic nerve just beneath the pia there was one small collection of glial cells with pleomorphic nuclei. No Toxoplasma organisms were seen. In the sciatic nerve the only definite abnormality was one small collection of lymphocytes around a vein. In sections of ventral and dorsal lumbar spinal roots and ganglia two small collections of lymphocytes and plasma cells without Toxoplasma organisms were observed.

Final Anatomical Diagnoses.—The final anatomical diagnoses were toxoplasmosis, disseminated, involving brain, heart, and striated muscle; bronchopneumonia, and biliary cirrhosis (slight).

ANIMAL INOCULATIONS AND SEROLOGIC STUDIES

Once the diagnosis had been established by the second muscle biopsy, a third biopsy specimen was taken on the 37th hospital day, after the patient had received sulfadiazine for 24 hours. The muscle was minced with a knife and gently macerated under aseptic conditions, and a sterile saline suspension of the muscle was allowed to stand until the heavier particles had settled. Smears of the supernatant fluid, stained with Giemsa's stain, contained several free-lying pseudocysts, one of which had ruptured, spilling its contents of individual Toxoplasma organisms. Aliquots (0.5 ml.) of the fluid were injected intraperitoneally into four hamsters, six mice, and one guinea pig. All but the guinea pig and two mice became acutely ill and died or were moribund within seven days. In all these animals Toxoplasma organisms were abundant in the peritoneal exudates. The hamsters showed a particularly massive plastic peritonitis. The strain was maintained by serial intraperitoneal transfers in mice and was also adapted successfully to the chorioallantoic membrane of the chick embryo upon the first attempt after the eighth mouse passage.

On the 52d day attempts were made to isolate Toxoplasma by the injection into mice of aliquots of cerebrospinal fluid, gastric washings, and buffy coat of blood. All these were unsuccessful. The patient was just concluding the course of sulfadiazine therapy when these samples were taken. Giemsa-stained smears of centrifuged sediment of one urine specimen showed no Toxoplasma.

At autopsy, specimens of heart, the lower lobes of both lungs, liver, spleen, kidney, psoas muscle, cerebrum, and medulla were removed aseptically. Samples of blood and cerebrospinal fluid were also obtained. Each specimen of tissue was macerated gently in saline solution and injected intraperitoneally into each of 10 mice. The blood and spinal fluid were injected in 0.5-ml. amounts without further treatment, using 10 mice for each specimen. Injections were given to a total of 110 mice; all but 6 died in 5 to 10 days, and representative animals taken from each group invariably had a profuse peritonitis, the exudate containing Toxoplasma organisms. Smears of peritoneal fluid were fixed in equal parts of ether and alcohol and stained with Giemsa's stain. The free-lying organisms in these smears appeared larger than those seen adjacent to the ruptured human pseudocysts. The organisms, after mouse or hamster passage, averaged 1.2 by 4.6 μ, but occasionally larger ovoid forms were encountered which measured up to 4.8 by 6.2 μ, and the nuclei in the passage strains were correspondingly larger than in human tissues (Fig. 4*D*). Representative animals that died of the induced infection were examined histologically, and Toxoplasma organisms and varying degrees of inflammatory reaction were demonstrable in every animal tissue examined except the kidneys, bone marrow, and retinae.

Sera obtained on the 36th and 43d hospital days showed neutralizing antibodies by the rabbit skin test.[19] Dye-test antibodies [20] were absent in a serum obtained on the 2d hospital day, but were present to a dilution of 1:16,384 on the 36th and 43d days, and to 1:32,768 on the 61st hospital day. Nonspecific thermolabile serum activator [20] was present in serum taken on the 61st hospital day to a dilution of 1:4. Blood for the latter determination was placed immediately into iced vessels; the serum was separated in the cold and stored at —70 C. until the tests were performed. The concentration of nonspecific thermolabile serum activator detected is one commonly found in human sera.[10]

COMMENT

Several features of this case are especially noteworthy. Of the greatest importance is the failure of the various therapeutic drugs to alter the outcome of the disease. This is in contrast to experimental evidence that sulfonamides,[21] aureomycin,[22] and sulfones [23] increase the rate of survival of animals infected with Toxoplasma. However, Toxoplasma may be isolated from treated, surviving animals for varying periods even when the organisms are not visible on histologic examination. There have been many attempts to treat congenital toxoplasmosis with appropriate drugs,[24] but it is difficult to judge the therapeutic effect, for in such cases most of the damage has been done before birth or the disease is chronic and the damage to the nervous system severe and irreversible. The patient of Sexton, Eyles, and Dillman [14] was treated with aureomycin for five days and with sulfadiazine for 36 hours before death, but such a short period of survival did not provide a satisfactory test of these therapeutic agents. However, the patient herein reported on was treated with aureomycin, penicillin and streptomycin, and sulfadiazine for sufficiently long periods to make it unlikely that therapy with these drugs greatly influenced the course of the disease. It must be conceded, however, that these drugs may have had some ameliorating effect because few fresh lesions were observed at the time of autopsy. Also it is possible that the administration of corticotropin decreased the patient's resistance to the infection and thereby decreased the effectiveness of some of the

19. Sabin, A. B., and Ruchman, I.: Characteristics of the Toxoplasma Neutralizing Antibody, Proc. Soc. Exper. Biol. & Med. **51**:1-6, 1942.

20. Sabin, A. B., and Feldman, H. A.: Dyes as Microchemical Indicators of a New Immunity Phenomenon Affecting a Protozoaan Parasite (Toxoplasma), Science **108**:660-663, 1948.

21. (*a*) Frenkel and Friedlander.[4f] (*b*) Warren, J., and Sabin, A. B.: Effect of Certain Antiprotozoal Drugs on Toxoplasma in Vitro and in Vivo, Proc. Soc. Exper. Biol. & Med. **51**:15-19, 1942. (*c*) Sabin, A. B., and Warren, J.: Therapeutic Effectiveness of Certain Sulfonamides on Infection by an Intracellular Protozoan (Toxoplasma), ibid. **51**:19-23, 1942. (*d*) Weinman, D., and Berne, R.: Therapeutic Cure of Acute Experimental Toxoplasmosis in Animals, J. A. M. A. **124**:6-8 (Jan. 1) 1944. (*e*) Adams, F. H.; Cooney, M.; Adams, J. H., and Kabler, P.: Experimental Toxoplasmosis, Proc. Soc. Exper. Biol. & Med. **70**:258-260, 1949. (*f*) Eichenwald, H.: Experimental Toxoplasmosis: II. Effect of Sulfadiazine and Antiserum on Congenital Toxoplasmosis in Mice, ibid. **71**:45-49, 1949. (*g*) Summers, W. A.: The Effects of Oral Administration of Aureomycin, Sulfathiazole, Sulfamerazine and 4,4'-Diamino-Diphenyl-Sulfone on Toxoplasmosis in Mice, Am. J. Trop. Med. **29**:889-893, 1949.

22. Summers.[21g] Kåss, E., and Steen, E.: Aureomycin Treatment of Acute Experimental Toxoplasmosis in Rabbits, Acta path. et microbiol. scandinav. **28**:165-168, 1951.

23. Summers.[21g] Cross, J. B.: Diasone and Promin as Therapeutic Agents in Experimental Toxoplasmosis, Proc. Soc. Exper. Biol. & Med. **76**:548-551, 1951.

24. Footnote 4*b*, *c*, *f*.

chemotherapeutic agents.[25] There are no data at present on the effect of the hormone on experimental toxoplasmosis. The only clinical effect that was observed was the diminution of fever, an effect that is clearly nonspecific [26] and by no means an indication that the pathologic process has been brought under control. It is of interest that alterations in the electrolytes of the serum that were observed by Sexton, Eyles, and Dillman were interpreted as indicating adrenocortical insufficiency,[14] and hence desoxycorticosterone was administered. The relationship between severe infection and adrenocortical insufficiency has been discussed elsewhere.[25] The response to corticotropin in this case makes it unlikely that adrenocortical insufficiency was present.

A second point clearly illustrated by our case is that toxoplasmosis can be acquired during adult life. There are now four instances of adult toxoplasmosis in which the serologic data leave no doubt that the infection had been recently acquired, i. e., two cases of Ström,[13] the case of Sexton, Eyles, and Dillman,[14] and the one reported here. In all four instances, control sera taken before or early in the course of the illness contained no antibody and subsequent determinations showed significant titers. The titers reported in the present case are high and similar to those which may be detected in congenitally infected infants and their mothers. One sample of serum, that obtained on the 63d hospital day, was tested for its content of nonspecific thermolabile activator, which was found to be present in normal concentrations. This finding suggests that the content of activator is unrelated to antibody titer and to the course of this infection. This is the first recorded instance of measurement of activator during the acute illness.

Since this patient had adequate amounts of both Toxoplasma antibody and its required heat-labile activator, death appears to have been a paradoxical solution to the illness. However, it has been long considered that intracellular parasites are at least in part protected from normal body defenses, and this principle is well illustrated by the present case.

It appears to be more than coincidence that three of the cases of acquired toxoplasmosis occurred in laboratory workers and that none of these had detectable antibody at the inception of the infection. It seems unwise, therefore, to permit workers to deal with Toxoplasma if they do not have antibodies for the organism. The relatively late development of antibodies in our case (none was detectable on the 12th day of the illness) should also be emphasized. Toxoplasmosis should not, therefore, be dismissed as a diagnostic possibility unless sera are taken well after the usual 14-day period—probably a month or more would be desirable as the minimal time interval between the taking of the acute phase and that of the late phase sera.

The proof that toxoplasmosis may be acquired in adulthood adds further substantiation to the commonly held concept that congenital toxoplasmosis is acquired *in utero* when the infection is present in the pregnant mother. The high incidence of

25. Kass, E. H., and Finland, M.: The Role of Adrenal Steroids in Infection and Immunity, New England J. Med. **244**:464-470, 1951.

26. Kass, E. H., and Finland, M.: Effect of ACTH on Induced Fever, New England J. Med. **243**:693-695, 1950. Recant, L.; Ott, W. H., and Fischel, E. E.: The Antipyretic Effect of Cortisone, Proc. Soc. Exper. Biol. & Med. **75**:264-266, 1950.

antibodies in mothers of infants with toxoplasmosis,[27] the occurrence of the disease in but one of many children of the same mother,[28] and the experimental demonstration of the capacity of Toxoplasma to cause congenital lesions are all consistent with this interpretation.[4d,e] There are also suggestions in the literature that organisms resembling Toxoplasma morphologically may be found by chance during the examination of tissues of patients with other diseases,[29] and there is ample evidence, confirmed by our findings, that Toxoplasma organisms may be isolated from tissues in which there is no histologic evidence of their presence.[21d]

The present case also exemplifies several prominent pathologic features of adult toxoplasmosis. These and previously recorded pathologic data are summarized in Table 1. It is evident that lesions and organisms may be extremely widespread, and that the central nervous system and major thoracic and abdominal viscera are commonly involved in fatal cases. Skeletal muscle lesions have heretofore not been described, but in only one of the other cases were negative findings in a specimen of

TABLE 1.—*Occurrence of Lesions and Organisms in Fatal Adult Toxoplasmosis*

Organ	Case 1 [6]	Case 2 [7]	Case 3 [7]	Case 4 [8]	Case 5 [14]	Case 6 *
Heart	TL	TL	TL	TL	TL	TL
Lungs	TL	TL	TL	T	L	T
Spleen	TL	TL	TL	T	T	T
Gastrointestinal tract	..	..	..	T	..	0
Pancreas	..	..	..	TL	..	L
Liver	TL	L	TL	TL	T	T
Adrenal glands	TL	..	..	0	0	0
Kidneys	TL	..	..	T	0	T
Genitourinary tract	..	..	..	..	..	0
Skeletal muscle	0	..	..	..	..	TL
Lymph node	TL	..	..	0	..	0
Skin	TL	L	..	TL	..	0
Central nervous system	TL	..	TL	TL	..	TL
Pituitary	..	..	..	TL	..	0
Complicating illness	Bartonellosis	..	..	..	..	..

* Case herein reported.

TL means Toxoplasma and lesions seen histologically; L, lesions but no Toxoplasma seen histologically, and T, Toxoplasma isolated or seen, without associated lesions.

muscle specifically mentioned. In the present case, the changes occurring in striated muscle were so striking and widespread that the potentialities of muscle biopsy as an additional diagnostic aid are apparent. The use of muscle biopsy in one of the reported cases of toxoplasmosis has been referred to previously.[9]

The lesions in striated muscle were more pronounced in some muscles than in others, but, in general, these consisted of foci of necrosis of sarcoplasm, with degenerative and proliferative sarcolemmal changes and with inflammation charac-

27. Sabin, A. B.: Complement Fixation Test in Toxoplasmosis and Persistence of Antibody in Human Beings, Pediatrics **4**:443-453, 1949.

28. Sabin, A. B., and Feldman, H. A.: Persistence of Placentally Transmitted Toxoplasmic Antibodies in Normal Children in Relation to Diagnosis of Congenital Toxoplasmosis, Pediatrics **4**:660-664, 1949.

29. Tomlinson, W. J.: Human Chronic Toxoplasmosis, Am. J. Clin. Path. **15**:123-127, 1945. Kean, B. H., and Grocott, R. G.: Asymptomatic Toxoplasmosis, Am. J. Trop. Med. **27**:745-751, 1947. Sulkin, S. E.; Lodowski, C. H., and Hartman, L. W.: Accidental Microscopic Finding of Toxoplasma in Human Blood, Texas Rep. Biol. & Med. **8**:47-51, 1950.

terized by the presence of many different types of cells. The infiltrate occasionally consisted of polymorphonuclear leucocytes, but more commonly was composed of macrophages and lymphocytes. Fibrin, vascular thrombi, and areas of fibroblastic proliferation could not be demonstrated. Pseudocysts were usually neither surrounded by inflammation nor associated with changes in the structure of muscle fibers, and free-lying forms were rarely seen in the inflammatory foci in our case. This was rather surprising in view of the extent of the polymyositis.

A comparison of the human with animal forms of the disease indicates the possibility that our patient's infection was entering a chronic stage in which free Toxoplasma organisms are rarely seen. The myocardial reaction was less marked, although organisms were more plentiful here than in any other tissue. Only a few interstitial areas containing macrophages and lymphocytes were seen, and these were not associated with fibroblastic proliferation and but rarely with evidence of degeneration of sarcoplasm. Pseudocysts without associated histologic change have been observed in congenital and adult toxoplasmosis, as well as in experimental animals.[30] The striking interstitial pneumonitis observed by Pinkerton and Henderson [7] was not seen in the present case. The pulmonary inflammation in our case and in that of Sexton and colleagues [14] was characteristic of the usual terminal bronchopneumonia. Minimal peripancreatic fat necrosis was observed, but no organisms were seen, unlike Nery Guimarães' case in which there were extensive pancreatitis and many organisms. The minimal periportal cirrhotic process noted in our case suggested biliary cirrhosis but appeared to be an old inactive process long antedating the present illness.

The neuropathologic picture in this case conformed with a focal embolic encephalomyelitis and in many respects resembled that seen in cases of subacute bacterial endocarditis. The glial clusters represented foci of tissue necrosis, and their size and close relationship to blood vessels suggested that they were caused by occlusion of prearterioles and arterioles. Blockage of larger vessels probably accounted for the few larger lesions. Since the cellular reaction varied from one lesion to another, it may be assumed that this process had continued over a considerable time, probably in several episodes over a period of weeks. It is improbable, considering the variation in size and the character of lesions, that an allergic encephalomyelitis of the perivascular type could have occurred, though the possibility of a secondary allergic reaction after the deposition of the organisms in the tissues is more difficult to decide. The hypothesis of embolic vascular occlusion would provide an explanation for the appearance of petechiae and the circulatory collapse that occurred several times during the clinical course of the disease. Proof of this embolic phenomenon by the finding of emboli or thrombi in blood vessels was not obtained in our case.

The inflammatory reaction is not readily classifiable as either suppurative or granulomatous. In some of the foci of tissue necrosis there were infiltrations of neutrophilic leucocytes, fibrin, and total necrosis of interstitial tissue and blood vessels to a degree seldom seen in bland infarcts. In others there was evidence that the inflammatory necrosis had occurred after an initial mononuclear reaction, for the faint outlines of closely packed macrophages could still be seen. Giant cells, closely packed epithelioid cells, or proliferating fibroblasts and calcific deposits

30. Sabin.[8] Footnote 4*b*, *d*, and *f*.

were not observed in any of the lesions. The brain lesions differed from those described by Wolf and associates [2] and others in this respect. It was impossible to decide whether these differences were a function of the age of the disease process or were related in some way to the age of the host. Since some of the lesions seen in this case were similar to those observed by Sabin [12] in his case of an apparently recently acquired juvenile encephalitis occurring in a 6-year-old boy, it is likely that the duration of the infection is the more important factor.

The occurrence of intact pseudocysts of Toxoplasma in tissues that were otherwise healthy in appearance indicates that in this form the organism is not capable of exciting an inflammatory reaction. As pointed out by others,[31] it seems that the outer membrane of the pseudocyst offers a barrier to the ready escape of the Toxoplasma or of the harmful products elaborated by them. Also, it is interesting in this regard that the cyst membrane is less permeable to certain stains than is the free organism.[31] It is difficult to decide from the microscopic sections whether the tissue changes developed only after rupture of the pseudocyst with liberation of its contents or were produced initially by hematogenous dissemination of large numbers of free Toxoplasma organisms, with the cysts forming later.

Clinicopathologic correlations are difficult when there is so widely disseminated a disease process as was encountered in the present case. The concentration of lesions in the diencephalon and upper midbrain, as well as the cerebrum, would afford an obvious explanation for the severe mental confusion and possibly for the bilaterally synchronous spike-and-wave formations seen in the electroencephalogram. The patient's clinical appearance could not be distinguished from that of an acute toxic psychosis, but the abnormalities of the cerebrospinal fluid and the development of slight focal neurologic signs permitted the exclusion of the latter diagnosis. A histologic correlation with the electrocardiographic evidence of myocarditis can be made, and it is possible that the widespread myositis accounts in part for the arthralgia and myalgia that were prominent initially. It is to be noted that severe muscle weakness did not occur, and in this respect the polymyositis of toxoplasmosis differs clinically from idiopathic dermatomyositis and polymyositis.

Analysis of the clinical findings in the uncomplicated cases of acquired and probably acquired toxoplasmosis suggests features that may be of clinical importance. It has been customary to divide the infection into four types: congenital, juvenile, rickettsiosis-like, and inapparent. However, analysis of the data indicates that, as with many such classifications, the lines of demarcation are poor. Thus, the congenital form differs from that acquired after birth in that cerebral calcifications and chorioretinitis are prominent in the former and the consequences of infection during the developmental period (anencephaly, microphthalmos, hydrocephalus, etc.) are necessarily more likely to induce major anatomic disturbances. In both forms of the disease, however, individual lesions may be similar, and a wide variety of organs may be involved. In both, also, the pathologic data suggest that hematogenous spread of the infection may occur.

In the proved cases of acquired toxoplasmosis the severity of the illness has varied from a mild, one-day febrile illness, with local adenopathy and no other distinguishing clinical features, to a fatal, widely disseminated infection, with a

31. Cross, J. B.: A Cytologic Study of Toxoplasma with Special Reference to Its Effect on the Host's Cell, J. Infect. Dis. **80**:278-296, 1947.

rickettsiosis-like rash, encephalitis, myocarditis, and polymyositis. An analysis of the more prominent clinical findings in the cases of proved or probable acquired infection in adults is presented in Table 2. The fatal cases have occurred in middle-aged adults, and the preponderance of infection in the female over that in the male is of interest in view of the problem of congenital toxoplasmosis. However, the

TABLE 2.—*Clinical and Laboratory Features of Six Cases of Adult Toxoplasmosis* *

Case No.	1 [7]	2 [7]	3 [13]	4 [13]	5 [14]	6 †
Age	50	43	22	22	47	60
Sex	M	F	F	F	F	F
Clinical Features						
Maculopapular rash	+	+	+	0	+	+
Fever	Remittent	Remittent	Remittent	One day	Remittent	Remittent
Headache	+	+	+	0	+	0
Weakness and malaise	+	+	+	?	+	+
Chilliness	+	+	+	0	+	+
Cough	+	0	0	0	+	+
Diarrhea	+	0	0	0	+	0
Arthralgia and myalgia	0	0	0	0	+	+
Conjunctivitis	0	0	+	0	0	0
Chorioretinitis	0	?	0	0	0	0
Mental status	Irrational terminally	Irrational terminally	Not disturbed	Normal	Delirium	Irrational late
Neurologic findings	Negative	Terminal areflexia; Oppenheim positive	Negative	Negative	Convulsions	Tremor and Babinski sign
Laboratory Results						
White blood cells	Normal	10,500	Leucopenia	....	Leucopenia	Normal
Hemoglobin	Normal	Normal	10.3 gm./100 ml.	....	11.5 gm./100 ml.	12.0 gm./100 ml.
Urine	Albumin and formed elements	Negative	Negative	....	Late albumin	Late albumin
Electrocardiogram	Myocardial disease	....	Myocarditis	....	....	Myocarditis
Cerebrospinal fluid	....	....	Pleocytosis and increased protein	....	Increased protein	Pleocytosis and increased protein
Antibodies	....	....	Appeared on 12th day	Negative on 14th day; positive at 3 mo.	Appeared on 4th day	Negative on 12th day; positive on 36th day
Roentgen Findings						
Pneumonitis	+	+	0	..	0	Terminal
Cerebral calcification	0	0	0	0	0	0
Outcome	Died on 6th day	Died on 18th day	Recovered; prolonged convalescence	Recovered; 1 day illness	Died on 10th day	Died on 75th day
Treatment	Symptomatic	Sulfanilamide, 3 days	"Sulfonamide," 8 days	"Sulfonamide," 1½ days	Aureomycin, 5 days; Sulfadiazine, 1½ days	Aureomycin; penicillin; streptomycin; sulfadiazine; ACTH; chloroquine

* Two adult cases have been omitted because the clinical features were obscured by coexistent infections with other organisms or were not accompanied with sufficient clinical data.[32]

† Case herein reported.

two fatal cases [32] that were omitted because of coexistent disease or insufficient clinical data both occurred in young adult males.

The clinical features of the severe rickettsiosis-like form of toxoplasmosis are well exemplified by our case. The fever, a maculopapular rash that spares the scalp, palms, and soles, headache, dry nonproductive cough, diarrhea, conjunctivitis, arthralgia and myalgia, lymphadenopathy, and pneumonitis are all characteristic and may be present initially or may occur during the course of the disease.

32. Pinkerton and Weinman.[6] Nery Guimarães.[8]

The significant laboratory findings are the presence of normal or low leucocyte counts with normal differential counts and the frequent occurrence of albumin and formed elements in the urine. Mild anemia may be present. Aside from the rash, the inconstant pneumonitis, and the occasional conjunctivitis and adenopathy, the results of the physical examination are not remarkable. The spleen and liver are not palpable. Ocular changes and cerebral calcifications are absent. As the disease progresses, electrocardiographic evidence of myocarditis and evidence of meningoencephalitis in the form of confusion, delirium, coma, pleocytosis, and increased protein in the spinal fluid may appear. A remittent fever is characteristic, and showers of petechiae or larger hemorrhagic lesions may occur. A muscle biopsy may be of diagnostic aid, as may injection of suspected tissue or blood into mice by the intracerebral or intraperitoneal route. Antibodies may not appear until more than two weeks after the onset of the disease.

In this severe form of the disease the prognosis is poor—only one case with recovery has been reported, and in that one there was a prolonged convalescence with evidence of myocarditis for two and a half months.[13] All gradations of cases with minimal symptoms, those in which encephalitis predominates, those in which the rickettsiosis-like features predominate, and those which combine all of the features of the disease are presumably possible.

The syndrome in its severest form appears to occur rarely, but milder forms of the disease are probably extremely common but remain, at present, unrecognized.[33] The drugs that are most effective experimentally are sulfadiazine, aureomycin, and perhaps the sulfones. Their clinical effectiveness remains to be demonstrated. Strŏm's first patient,[18] with severe clinical disease, recovered after treatment with sulfonamides. Our patient failed to manifest any significant clinical benefit from therapy with these drugs, antibiotics, or an antimalarial drug.

SUMMARY AND CONCLUSIONS

Toxoplasmosis is being recognized with increasing frequency in children as a congenital illness, but evidence that the infection may be acquired later in life, particularly during the adult years, has only recently been accumulated.

A case of this disease presenting certain unusual features is described. The patient was an elderly woman, and the source of the infection could not be determined. The illness took the form of a "spotted fever." The diagnosis was made from the histologic appearance and animal pathogenicity of organisms seen in a muscle biopsy specimen. The patient was treated, at various times, with full courses of aureomycin, penicillin, streptomycin, sulfadiazine, corticotropin, and chloroquine. Although treatment with these drugs may have modified the course of the disease, for at autopsy many of the lesions were apparently healing, the patient died. Serial antibody studies indicated that the infection was acquired. Studies of the "nonspecific activator" showed it to be present in normal concentrations in the patient's serum.

33. Since this article was submitted for publication, we have seen two reports (Siim, J. C.: Acquired Toxoplasmosis: Report of 7 Cases with Strongly Positive Serologic Reactions, J. A. M. A. **147**:1641-1645 [Dec. 22] 1951; Magnusson, J. H.: Symptoms of Toxoplasmosis, Nord. med. **45**:344-348, 1951; abstracted, J. A. M. A. **146**:1169 [July 21] 1951) which further indicate that toxoplasmosis may be acquired and that the infection may be associated with mild symptoms.

A detailed clinical history and complete autopsy observations are presented, with analysis of pertinent findings in similar cases. The autopsy showed widespread polymyositis, severe damage to the central nervous system in the form of a meningoencephalomyelitis, and myocarditis. Toxoplasma organisms were isolated from heart, lung, liver, kidney, spleen, cerebrum, medulla, blood, and cerebrospinal fluid at autopsy, but unequivocal histologic lesions were demonstrated only in the brain, myocardium, and striated muscle.

The clinical syndrome in adult toxoplasmosis consists of fever, maculopapular rash sparing the scalp, palms, and soles, and headache. There may be cough, arthralgia and myalgia, lymphadenopathy, pneumonitis, and conjunctivitis, but cerebral calcifications and chorioretinitis are absent. Leucopenia or normal leucocyte counts occur. The distribution of the myositis, the myocarditis, the lesions in the central nervous system, and the petechial skin eruptions all are indicative of a hematogenous spread of the infecting agent. Antibodies may not appear until late in the course of the disease.

A few persons with diagnosed toxoplasmosis have recovered, and some of these have had a very mild infection. The relatively high incidence of antibodies suggests that toxoplasmosis is a common disease which usually assumes the form of a mild infection with few symptoms. Rarely will such a florid example of the disease as the one reported here be encountered in an adult.

PRIMARY HYPERPARATHYROIDISM

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NORRIS,[1] in 1947, reported on 336 cases of parathyroid adenoma which he had been able to collect from the literature between 1903 and 1947. He suggested that during the subsequent 10 years all cases of parathyroid adenoma warranted publication. With this in mind, we are presenting a summary of all the cases of primary hyperparathyroidism that have been seen at the Lahey Clinic since the first case was diagnosed in 1933; eight of these cases have been reported previously.[2]

No attempt will be made to review the history of the knowledge of parathyroid diseases or the extensive literature on parathyroid physiology. The history of hyperparathyroidism has been reviewed in an interesting fashion by Albright,[3] and the pathophysiology has been discussed in detail by Albright and Reifenstein.[4]

Although there is some diversity of opinion concerning the basic mechanism through which the parathyroid hormone acts, the ultimate effect of an excess of the hormone is to increase the transport load of serum calcium, with the production of systemic symptoms caused by the elevated serum calcium and of secondary symptoms from deposition of calcium in certain tissues and withdrawal of calcium from the bones. The varied symptomatology that may result is diagramed in Figure 1.

Systemic symptoms apparently are the result of the elevation in the serum calcium level. These symptoms (*1*, Fig. 1) are vague, simulate remarkably those of many abnormal functional states, and are frequently misinterpreted for long periods. There is nothing diagnostic about weakness, easy fatigability, constipation, nausea, vomiting, anorexia, or cramp-like abdominal pain. Nevertheless, they may be prominent symptoms in hyperparathyroidism, and, in rare instances in which neither renal disease nor abnormalities of the bone are present, they may represent the sole symptomatic manifestations of the disease.

From the Department of Medicine, The Lahey Clinic.

1. Norris, E. H.: Collective Review: Parathyroid Adenoma; Study of 322 Cases, Internat. Abstr. Surg. **84**:1-41, 1947; in Surg., Gynec. & Obst., Jan., 1947.

2. (*a*) Lahey, F. H., and Haggart, G. E.: Hyperparathyroidism: Clinical Diagnosis and the Operative Technique of Parathyroidectomy, Surg., Gynec. & Obst. **60**:1033-1051 (June) 1935. (*b*) Murphy, R.: Hyperparathyroidism, Lahey Clin. Bull. **6**:112-118 (April) 1949. (*c*) Bell, G. O., and Arnold, W. T.: Primary Hyperparathyroidism: Report of 2 Unusual Cases, ibid. **6**:197-203 (Jan.) 1950.

3. Albright, F.: Page out of the History of Hyperparathyroidism, J. Clin. Endocrinol. **8**:637-657 (Aug.) 1948.

4. Albright, F., and Reifenstein, E. C., Jr.: The Parathyroid Glands and Metabolic Bone Disease: Selected Studies, Baltimore, Williams & Wilkins Company, 1948, p. 393.

The excretion of the excessive calcium and phosphorus may lead to the development of symptoms and signs referable to the urinary tract (*2*, Fig. 1). In the early stages, the symptoms of polyuria and polydipsia may be of sufficient intensity to mimic diabetes. With the subsequent development of renal calculi or calcinosis, symptoms of renal colic, hematuria, secondary infection, and, finally, renal insufficiency may appear.

The secondary effect on the bony structures leads to a variety of abnormalities (*3*, Fig. 1): fractures, deformities, cysts, and tumors. Pain is a common and early symptom and may be misinterpreted as neuritis or arthritis. Of considerable interest are the changes which may occur in the jaws, such as malocclusion, separation of the teeth, tumors, cysts, and disappearance of the lamina dura.

In addition to the deposition of calcium in the kidneys, metastatic calcification may occur in blood vessels, conjunctivae and corneae,[5] and other tissues (*4*, Fig. 1).

PRESENT STUDY

The present study consists of an analysis of 25 cases of primary hyperparathyroidism diagnosed at the Lahey Clinic between 1933 and July, 1951 (Table 1).

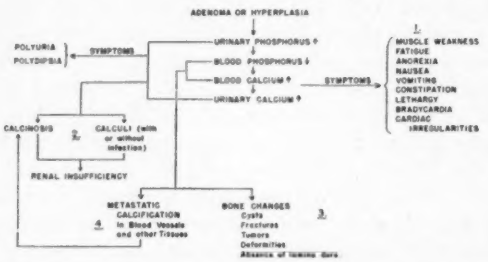

Fig. 1.—Relation of chemical findings to development of symptoms of primary hyperparathyroidism.

Of these 25 cases, 24 were proved by exploration and 1 was proved at autopsy. During this same period there were four additional cases in which the diagnosis was established clinically, but exploratory operation was not performed for various reasons. One additional case was diagnosed clinically, and a tumor was not found at exploration, but the patient is still considered to have hyperparathyroidism. Two nonfunctioning parathyroid tumors also have been discovered, one an adenoma and the other an adenocarcinoma. The statistics included in this report are based upon the 25 proved cases.

Sex Distribution.—There were 19 women and 6 men in the series, that is, a ratio of 3.2 women to 1 man. Although there has been some variation in the sex ratio in individually published series, Norris' review [1] of 317 cases collected from the literature showed a ratio of 3 women to 1 man.

Age Distribution.—The patients' ages varied from 16 to 74 years. Fourteen patients, or 56%, were between 30 and 60 years of age at the time of diagnosis.

5. Fleischner, F. G., and Shalek, S. R.: Conjunctival and Corneal Calcification in Hypercalcemia: Roentgenologic Findings, New England J. Med. **241**:863-865 (Dec. 1) 1949.

TABLE 1.—*Summary of Data on Twenty-Five Proved Cases of Primary Hyperparathyroidism*

Case No.	Year	Age at Diagnosis, Yr.	Sex	Duration of Symptoms, Yr.	Locus of Tumor*	Size of Tumor, Cm.	Skeletal Changes, Group†	Lamina Dura	Renal Calculi	Gastrointestinal Symptoms	Lowest Calcium, Mg./100 Cc.	Highest Phosphorus, Mg./100 Cc.	Lowest Alkaline Phosphatase, Bodansky Units	Length of Follow-Up, Yr.	Comment
1	1933	62	F	5	LL	3.7 × 1.9	II	—	0	0	13.3	2.3	7.5	3.0	.....
2	1933	53	F	5	RL	1.0	II	0	0	0	12.5	3.5	10.2	18.0	.....
3	1933	74	F	10	RU	0.7	I	—	0	+	11.3	3.0	7.2	1.5	Adenoma embedded in thyroid
4	1934	44	F	2	RLL	3.5 × 2.0 × 0.7	I	—	0	0	14.4	3.5	35.0	11.0	.....
5	1934	52	F	12	RLL	1.5 × 2.0	II	—	0	+	13.4	2.1	44.8	13.0	Paget's disease; numerous exploratory abdominal operations
6	1940	29	F	4	Ab	.....	I	—	+	0	14.0	2.8	17.3	10.0	4 explorations; tumor in mediastinum; biopsy: giant-cell tumor; multiple dental extractions and excision of jaw cysts
7	1941	34	M	3	Ab	1.5	II	—	+	0	12.0	3.7	5.0	9.0	Adenoma beneath left sternoclavicular articulation
8	1941	51	F	14	RLA	2.0 × 1.5	I	—	+	+	12.0	2.6	15.8	6.0	Duodenal ulcer; Paget's disease
9	1944	56	F	1	RLP	4.9 × 2.4 × 1.5	III	+	0	0	14.8	2.6	3.7	1.0	.....
10	1945	70	M	23	RLP	3.0 × 3.0 × 4.0	I	—	+	0	13.9	5.0	8.9	....	Prostatic hypertrophy; uremia; diagnosis made clinically; proved by autopsy
11	1946	61	F	3	LU	2.0 × 1.0 × 0.5	II	—	0	+	11.3	2.6	3.4	0.5	.....
12	1946	53	F	3	LL	3.5	I	—	+	0	14.4	3.6	46.0	5.0	Nitrogen retention with good postoperative result
13	1947	61	F	3	LL	2.0	I	—	0	0	12.0	4.2	20.8	0	One previous exploration; poor kidney function
14	1948	33	F	3	RU	2.8 × 1.8 × 1.8	I	—	+	0	12.6	2.0	8.2	3.5	Dental extractions for arthritis; lump in jaw noted at extractions
15	1948	18	M	1	RL	2.0 × 1.0	II	+	0	0	13.9	2.9	8.2	2.5	Postoperative psychosis
16	1948	31	F	1	RL	2.0 × 2.0 × 0.9	I	0	+	0	14.5	3.9	4.8	3.0	One previous exploratory operation; dental extractions; curettage of jaw cyst
17	1948	48	F	3	RL	.....	II	—	0	0	11.9	3.1	10.0	3.0	Biopsy: giant-cell tumor; one previous exploratory operation
18	1948	22	F	1	LU	2.0	III	+	0	+	14.3	2.4	2.8	0.5	Diabetic-like syndrome
19	1948	34	F	3	RL	3.0 × 2.0 × 1.8	I	0	0	0	14.4	2.4	8.2	2.5	Biopsy: giant-cell tumor
20	1949	63	F	1	RU	.....	II	0	+	..	14.5	2.2	10.2	....	Adenoma embedded in thyroid; adenoma of parathyroid with invasion; acute pancreatitis postoperatively
21	1950	37	M	5	.....	Hyperplasia of 4 glands	III	+	+	+	11.0	2.5	1.8	1.0	.....
22	1950	34	M	2	LL	3.0 × 1.5 × 0.6	III	+	+	0	12.3	3.1	3.8	0.7	.....
23	1951	29	F	3	RL	4.0 × 2.5 × 2.0	I	0	0	0	13.6	2.0	33.9	....	Jaw cyst curetted by dentist
24	1951	16	M	1.5	LLP	1.5 × 0.8 × 0.4	II	—	+	0	12.4	3.8	7.3	...	.....
25	1951	46	F	13	RL	1.5	III	+	+	+	12.0	3.3	2.6	....	Previous duodenal ulcer

* RU indicates right superior; LU, left superior; RL, right inferior; LL, left inferior; RLL, right inferior lateral; RLA, right inferior anterior; RLP, right inferior posterior; Ab, aberrant.

† Group I, classic osteitis fibrosa cystica; Group II, minimal or atypical changes; Group III, no skeletal disease.

The significant feature is the fact that the distribution according to age is very wide and, therefore, of little importance diagnostically (Table 2).

Location of Tumors.—The location of the tumors is of great importance to the surgeon during exploration. The most complete study is that of Norris,[1] who found 251 cases in the literature in which the site of the tumor was given. In his study, the loci of the tumors were about equally divided between the right and the left sides (52.6% were on the right and 47.4% on the left). One hundred ninety-four cases could be studied further, and the location of the tumors showed the following frequencies in relation to the lobes of the thyroid gland: right upper lobe, 9.1%; left upper lobe, 7.1%; right lower lobe, 42.7%, and left lower lobe, 41.1%. Single adenomas in aberrant positions were observed in 30 instances; 19 of these were in the mediastinum, 9 within the thyroid, and 2 behind the esophagus.

The location of the tumors in the present series of 25 proved cases is shown in Table 3. In two patients the adenomas were embedded in the substance of the thyroid gland, and each of them was in relation to a superior lobe. The finding of two cases of intrathyroid adenomas suggests that they are not rare and that the possibility of such a locus should always be considered when exploration of the

TABLE 2.—*Age Distribution*

Decade	Number of Cases
Second	2
Third	3
Fourth	6
Fifth	3
Sixth	5
Seventh	4
Eighth	2

neck fails to reveal an adenoma in a suspected case of hyperparathyroidism. Lahey and Haggart [2a] called attention to this in 1935, and Lahey [6] reemphasized it in 1945. Recently, its significance was discussed again by Black and Haynes.[7] In two patients the adenoma was located in an aberrant position, and in one patient hyperplasia of four parathyroid glands was found.

Pathologic Characteristics of Tumors.—In the patient with parathyroid hyperplasia, four glands were identified at operation. A right inferior and a left inferior gland were excised. Pathologic interpretation of both glands was hyperplasia primarily involving chief cells. In the remaining patients single adenomas were identified. The dimensions of the excised glands are recorded in Table 1. They were variously described as yellow-brown, tan, yellow-red, amber, or gray-tan. In all instances they were encapsulated. Frequently, cyst-like spaces and hemorrhagic areas were noted in the cut sections. In one case invasion of the capsule was described. Histologically, the tumors were considered either to consist of chief cells predominantly or to be of a mixed-cell type.

6. Lahey, F. H.: Earlier Diagnosis of Hyperparathyroidism, Lahey Clin. Bull. **4**:66-72 (Jan.) 1945.

7. Black, B. M., and Haynes, A. L.: Intrathyroid Hyperfunctioning Parathyroid Adenomas: Report of 2 Cases, Proc. Staff Meet., Mayo Clin. **24**:408-413 (Aug. 3) 1949.

Duration of Symptoms.—The estimated duration of symptoms before a diagnosis was made varied widely. The shortest duration was 1 year and the longest 23 years. The majority of the patients had had symptoms for two to five years before the diagnosis was established.

Symptoms.—There was a wide variation in the presenting complaints, although symptoms referable to the renal and skeletal systems predominated. Table 4 shows the frequency of the chief complaints in this series.

A better understanding of the symptoms of hyperparathyroidism is obtained when attention is directed toward the total complaints, rather than the presenting complaints. Table 5 shows the relative frequency of complaints in this series and demonstrates the prominence of symptoms not related to the kidneys or skeletal

TABLE 3.—*Location of Parathyroid Tumors*

Location	Number of Cases
Right superior lobe of thyroid	3
Left superior lobe of thyroid	2
Right inferior lobe of thyroid	12
Left inferior lobe of thyroid	5
Low in neck on left	1
Mediastinum	1
Hyperplasia of 4 glands	1

TABLE 4.—*Frequency of Presenting Symptoms*

Symptoms	Number of Cases
Bone pain	9
Renal colic	5
Systemic symptoms	3
Gastrointestinal symptoms	3
Fractures	1
Muscle pain	1
Cysts of jaw	1
Urinary symptoms	1
Skin disease	1

system. Nine patients had gastrointestinal symptoms that were considered significant features of their disease. Of these, two had proved duodenal ulcers. In addition, there was one patient without any gastrointestinal symptoms for whose condition the clinical diagnosis of hyperparathyroidism was made. This patient died of a perforated duodenal ulcer before parathyroidectomy could be performed. The gastrointestinal symptoms included anorexia, nausea, vomiting, cramp-like abdominal pain (at times severe), ulcer-like symptoms, and constipation.

Skeletal Disease.—Historically, skeletal disease ranks first among the findings in hyperparathyroidism. However, as diagnostic acumen has improved, the frequency of the diagnosis in patients without skeletal disease has increased. Of the 25 patients in this series, 20 showed evidence of bone disease, as characterized by osteoporosis with or without bone cysts. Deformities of bones were noted in 14 patients, cysts in 11, and fractures in 6.

Cysts of the mandible were of significance in four patients. One of these had had four teeth extracted and a curettage of a cyst of the mandible one year pre-

viously and was seen at the clinic with the chief complaint of recurrence of a lump in the mandible. The other three had numerous other complaints but gave histories of previous dental extractions and excisions of cysts of the mandible.

The disappearance of the lamina dura has frequently been noted in patients with hyperparathyroidism. Information concerning the lamina dura was available for 11 patients in this series, and in only 5 was it absent. In the six patients in whom the lamina dura was present, five were without evidence of bone disease, and in each of these the alkaline phosphatase level was normal. The remaining patient had minimal bone disease with a slightly elevated alkaline phosphatase level and had noted symptoms for only one year. One patient had had symptoms of hyperparathyroidism for 13 years, yet bone disease was not evident, the lamina dura was present, and the alkaline phosphatase was repeatedly within the normal range. It appears, therefore, that the lamina dura may be present when bone disease is not evident or when the skeletal involvement is of minimal degree and of short duration.

TABLE 5.—*Frequency of Complaints*

Complaints	Number of Cases
Systemic Symptoms	
Weakness, fatigability	10
Gastrointestinal	9
Muscle pain	5
Weight loss	3
Genitourinary Symptoms	
Renal colic	7
Frequency, nocturia	6
Polydipsia	5
Hematuria	1
Dysuria	1
Bone Symptoms	
Bone pain	13
Deformities	4
Loss of stature	4
Lump in jaw	4
Fractures	2

The association of hyperparathyroidism and Paget's disease (osteitis deformans) in the same patient has been commented upon by Albright and Reifenstein.[4] In this series, there were two patients in whom the two diseases were coexistent. Both were women, 49 and 52 years of age, respectively. After excision of the parathyroid adenomas, the blood calcium and phosphorus values returned to normal. The alkaline phosphatase values fell below the preoperative levels but never returned to normal. Long-term follow-up observations were available on both patients. One was examined 6 years and the other 13 years after parathyroidectomy. In each patient, the blood chemical findings at the final follow-up examination were consistent with those in Paget's disease and roentgenographic studies showed marked progression of the disease.

For three patients diagnoses of giant-cell tumor of the bone had been made on the basis of previous bone biopsies. For one patient a diagnosis of giant-cell tumor was made after biopsy of a lesion in the right tibia. The presence of hyperparathyroidism had been suspected elsewhere but was not confirmed by repeated blood chemical studies. The appearance on several bone roentgenograms was consistent

with the diagnosis of osteitis fibrosa cystica, and this diagnosis was confirmed by chemical determinations at the clinic. This case demonstrated the importance of repeated determinations of the blood calcium, phosphorus, and alkaline phosphatase levels, in different laboratories if necessary, before discarding the diagnosis if there is good clinical evidence in favor of it. In a second patient the diagnosis of giant-cell tumor was made one year previously after biopsy of a lesion in the left humerus. Radiation therapy of this area was given without relief of the symptom of bone pain and without change in the appearance of the lesion. The third patient had had multiple exploratory operations without an adenoma being found. After a bone biopsy, the results of which were reported as consistent with a giant-cell tumor, an aberrant adenoma was found in the mediastinum on repeated exploration elsewhere.

Keating and Cook [8] classified patients with hyperparathyroidism on the basis of the degree of skeletal involvement. Their classification consists of three groups: Group I, classic osteitis fibrosa cystica; Group II, minimal or atypical bone disease, and Group III, absence of skeletal disease. Of their series of 24 patients, 29% were in Group I, 38% in Group II, and 33% in Group III. On the basis of this classification, in the present series 11 patients (44%) had osteitis fibrosa cystica, 9 (36%) had minimal or atypical bone changes, and 5 (20%) were without skeletal disease.

Renal Calculi.—Twelve patients were noted to have renal calculi. Of these, five patients had presenting symptoms directly ascribed to the calculi. In only one patient were the stones asymptomatic. Four patients had evidence of renal insufficiency, as shown by an elevated nonprotein nitrogen level. One of these was particularly interesting; at the time of operation the patient had hypertension, marked osteitis fibrosa cystica, a left renal calculus, markedly elevated serum alkaline phosphatase level, anemia, diminished renal function as evidenced by poor visualization on intravenous pyelographic studies, and a blood nonprotein nitrogen level of 70 mg. per 100 cc. She has been examined frequently during the four and one-half years since operation. Although the blood nonprotein nitrogen level has varied between 58 and 105 mg. per 100 cc., the patient consistently has felt well.

On the basis of the association of renal disease and bone disease, Albright and Reifenstein [4] divided patients having hyperparathyroidism into four groups: Group A, those with bone disease and without kidney disease; Group B, those with bone disease and with kidney disease; Group C, those without bone disease and with kidney disease, and Group D, those without bone disease and without kidney disease. In the series of cases collected by Norris,[1] skeletal lesions predominated, while in the 64 cases from the Massachusetts General Hospital series referred to by Albright and Reifenstein [4] renal lesions were more frequent. A comparison of the present series with those mentioned above is given in Table 6.

Blood Chemical Determinations.—The values of the blood calcium, phosphorus, and alkaline phosphatase play such a great role in the preoperative verification of the diagnosis of hyperparathyroidism that it is important to emphasize the wide range that may occur. The blood calcium need not be markedly elevated. Albright and Reifenstein [4] called attention to the fact that if parathyroid extract is given to a normal person the urinary calcium may be doubled without producing a significant

8. Keating, F. R., Jr., and Cook, E. N.: Recognition of Primary Hyperparathyroidism: Analysis of 24 Cases, J. A. M. A. **129**:994-1002 (Dec. 8) 1945.

change in the serum calcium level. In those patients whose serum calcium level is not greatly elevated, it is extremely important to determine the serum protein level, since a lowered serum protein level may mask an otherwise elevated serum calcium level. The presence of renal insufficiency may cause an elevation of the phosphorus value with or without an associated depression of the calcium value. In the absence of bone disease, the alkaline phosphatase value is normal. If Paget's disease is coexistent, the phosphatase value may be excessively high. Table 7 shows the range between the lowest and the highest values in this series after all cases were eliminated in which there was any question of renal insufficiency or Paget's disease.

Postoperative Complications.—The chief complication during the postoperative period is the development of tetany, which may vary from mild symptoms of a transient nature requiring no therapy to severe symptoms necessitating treatment for weeks or months. Ordinarily, tetany is not a serious complication. It may develop within the first 24 hours after operation and may occur in any patient,

TABLE 6.—*Association of Renal Calculi and Bone Disease*

Group [4]	Bone Disease	Kidney Disease	Norris' Series,[1] 314 Cases	Albright and Reifenstein's Series,[4] 64 Cases	Present Series, 25 Cases
A	+	0	191	11	11
B	+	+	101	24	9
C	0	+	17	28	3
D	0	0	5	1	2

TABLE 7.—*Range of Blood Chemical Determinations*

Bone Disease	Calcium, Mg./100 Cc.	Phosphorus, Mg./100 Cc.	Alkaline Phosphatase, Bodansky Units
Absent	11.0-16.3	1.6-3.3	1.8- 8.4
Present	11.3-16.0	1.4-3.9	3.4-35.0

although it is slightly more frequent in patients in whom the preoperative calcium or alkaline phosphatase levels, or both, are markedly elevated. In this series, 13 patients had some degree of postoperative tetany. Of these, only three had preoperative serum calcium values below 14 mg. per 100 cc. and eight had alkaline phosphatase values of less than 20 Bodansky units. Of the 11 patients without postoperative tetany, 7 had serum calcium levels below 14 mg. per 100 cc. and 8 had alkaline phosphatase values of less than 20 Bodansky units.

Two patients displayed serious postoperative complications, one a postoperative psychosis which was concomitant with the postoperative fall in serum calcium value to a normal level, the other an acute necrotizing pancreatitis with an accompanying severe tetany.

Follow-Up Observations.—In the 24 patients in this series on whom operation was performed, the period of follow-up observation varied from less than 1 year to 18 years. The over-all follow-up evaluation was excellent. One patient with bilateral renal calculi continued to pass stones for 10 months but noted a decrease in the frequency of attacks. One patient in whom a postoperative psychosis devel-

oped was reported two years later to be physically in good condition but somewhat erratic in behavior. A third patient who had manifested marked psychoneurotic behavior preoperatively continued unchanged through a follow-up period of 13 years.

ILLUSTRATIVE CASES

A few case histories are given below to illustrate the wide variety of symptoms that are evident in patients with hyperparathyroidism.

Diabetic-like Symptoms.—CASE 18.—A 22-year-old woman entered the clinic because of an unexplained weight loss of 28 lb. (12.7 kg.) within the preceding year. Her appetite had been poor, and on occasion abdominal distress and vomiting were noted. During the same interval polydipsia, frequency of urination, polyuria, and increasingly severe muscular weakness developed.

No abnormalities, except for evidence of weight loss and marked muscular weakness, were revealed by a physical examination.

Laboratory studies disclosed that the total blood protein was 6.2 gm., albumin, 3.3 gm., globulin, 2.9 gm., calcium, 14.2 to 15.8 mg., and phosphorus, 1.6 mg. to 2.4 mg., per 100 cc. Alkaline phosphatase was 2.8 to 4.2 Bodansky units. Repeated urine tests showed a persistently positive reaction to the Sulkowitch test.

Roentgenograms of the skull were normal. The lamina dura was present. Except for duplication of the right kidney, no abnormalities were demonstrated on intravenous pyelograms.

Exploration of the neck revealed a bean-shaped, soft, pale, tan, encapsulated adenoma on the inferior aspect of the upper pole of the left lobe of the thyroid gland. This was resected without difficulty. Postoperatively, the patient experienced some mild tingling of the hands, feet, and circumoral area, which was readily controlled with calcium gluconate given intravenously.

Six months after operation she reported that she felt well, had regained her lost weight, and was free from symptoms. The blood calcium was 9.7 mg. and the phosphorus was 4.1 mg. per 100 cc.

Primarily Systemic Symptoms; Late Postoperative Tetany.—CASE 9.—A 56-year-old woman was seen at the clinic with the chief complaint of stiffness of the thighs of one year's duration. On exertion some aching was noted in the same areas. Results of laboratory studies done elsewhere suggested hyperparathyroidism.

No significant abnormalities were noted on physical examination, except that the right lobe of the thyroid gland was enlarged and nodular.

Laboratory examination revealed 14.8 to 16.3 mg. of calcium and 2.4 to 2.6 mg. of phosphorus per 100 cc. Alkaline phosphatase was 3.7 to 8.4 Bodansky units. The Sulkowitch test gave a markedly positive reaction after three days on a low calcium regimen.

Roentgenographic examination of the skull, right knee, feet, hands, chest, ribs, and pelvis did not reveal any abnormalities, except for some trabeculation of the upper half of the right patella suggestive of Paget's disease and a thin cranial vault. The lamina dura was present. Intravenous pyelograms did not demonstrate any calculi, but the concentration of the dye was poor.

At operation, a pale pink and gray-brown adenoma was found just posterior to the inferior pole of the right lobe of the thyroid gland.

Postoperatively, while in the hospital, the patient did quite well. Upon leaving the hospital, she became nervous and hysterical, and a definite personality change developed. She was readmitted to the hospital 12 days after discharge with symptoms of tetany. The blood calcium on readmission was 7.8 mg. per 100 cc. Therapy consisted of calcium lactate and dihydrotachysterol ("A. T. 10") given orally; response was excellent.

On follow-up examination one year later the calcium was 10.3 mg. and the phosphorus 4.2 mg. per 100 cc., and alkaline phosphatase was 3.6 Bodansky units. A roentgenogram of the skull showed a normal condition. The patient felt well and was without symptoms of tetany, and her personality had returned to its preoperative state.

Duodenal Ulcer; Paget's Disease.—CASE 8.—A 49-year-old woman was first seen at the clinic in 1939, with the chief complaint of gnawing epigastric pain of three years' duration. At 37 years

of age she had had a bladder lithotomy. Subsequent difficulty with bladder calculi had not developed. A duodenal ulcer was demonstrated by a roentgenogram of the duodenum. Throughout the next two years she had numerous episodes of epigastric pain, nausea, and vomiting, usually relieved by ingestion of milk, alkalis, and aluminum hydroxide gel (amphojel®). On one occasion a period of hospitalization for ulcer management was required.

In 1941 some urinary symptoms developed which led to the investigation of the urinary tract. Calculi were not demonstrated, but it was noted that the bony structures were denser than normal. The blood calcium varied from 12.0 to 13.0 mg. and the phosphorus from 2.0 to 2.6 mg. per 100 cc. The alkaline phosphatase ranged from 15.8 to 16.4 Bodansky units. The total blood protein was 7.0 gm. per 100 cc.

Roentgenographic examination of the skull showed a dense cranial vault with obliteration of the table markings and numerous punched-out areas, causing a mottled appearance; that of the lumbosacral portion of the spine and the pelvis, loss of the usual bony trabeculations; that of the bones of the arms and legs, osteoporosis and cysts; that of the hands, decalcification of bones, with a cystic area in the terminal phalanx of the right third finger, and that of the feet, decalcification and cysts.

On exploration, an adenoma was found on the anterior aspect of the right inferior lobe of the thyroid gland and was removed. Postoperatively, evidence of tetany did not develop.

Nine months later, the patient felt well and abdominal symptoms had not recurred. Roentgenograms of the skull, lumbosacral portion of the spine, and pelvis revealed increased density, monophasic changes of Paget's disease in the skull, and diphasic changes in the spine and pelvis. The blood calcium was 10.6 mg. and the phosphorus 4.3 mg. per 100 cc.; alkaline phosphatase measured 10.3 Bodansky units.

The patient's course was followed until 1947 (six years after operation), when she died of a cerebral thrombosis. Throughout the follow-up period, during which there had been various symptoms related to the development of pseudobulbar palsy, gastrointestinal symptoms had not recurred.

Gastrointestinal Symptoms, Severe; Paget's Disease; Prolonged Tetany.—CASE 5.—A 52-year-old white woman gave a 12-year history of recurrent episodes of severe abdominal pain, with vomiting and obstinate constipation. Numerous abdominal operations had been performed for the relief of this pain without success, and recourse had been made to opiates.

On physical examination, the patient was mentally confused, showed numerous healed scars from incisions in the abdominal wall, diffuse abdominal tenderness on palpation, and extreme anterolateral bowing of the tibiae.

Laboratory examination revealed that the blood calcium was 13.4 to 14.1 mg. and the blood phosphorus 2.0 to 2.1 mg. per 100 cc. Alkaline phosphatase was 44.8 Bodansky units.

Roentgenographic study of the skull showed a number of mottled, irregular areas of increased density with some actual thickening of bone; that of the spine, mushrooming of the first lumbar vertebra with increased density of the bone; that of the sacrum, increased density with prominent bony trabeculations; that of the left tibia, bowing with thickened cortex and coarse trabeculations, and that of the kidney, ureter, and bladder, absence of calculi. The interpretation was Paget's disease of the bone.

An exploratory operation was performed, and a partly encapsulated, amber-colored adenoma was demonstrated in relation to the lateral aspect of the right inferior lobe of the thyroid gland.

On the third postoperative day, tetany was noted and treated with calcium lactate and parathormone. The blood calcium at this time was 7.8 mg. and the phosphorus 2.4 mg. per 100 cc. As long as treatment was continued, the tetanic symptoms were controlled, but the patient never was able to dispense with the treatment.

During the first two years of her follow-up period, there was marked improvement in her mental attitude but complaints of pain and "bowel trouble" continued. Thirteen years later, the patient was found to have a poor appetite and spells of unconsciousness. Blood calcium (under treatment) was 8.2 mg. and phosphorus 3.6 mg. per 100 cc.; alkaline phosphatase was 13.7 Bodansky units. Roentgenograms of the skull, sacrum, lumbosacral portion of the spine, and pelvis showed an appearance consistent with advanced Paget's disease and platybasia. It was thought that addiction to opiates contributed to her symptoms.

Bone Disease Without Calculi; Postoperative Psychosis.—CASE 15.—An 18-year-old youth entered the clinic with the chief complaint of cramp-like pain in the calf of the right leg which had first developed 11 months previously, immediately after an appendectomy. Eight months before he came to the clinic a roentgenogram had demonstrated a "curvature of the spine," and the patient had been placed in a body cast for three months. Subsequently, numbness and tingling in the toes of the right foot were noted.

On examination, the patient appeared to be healthy. He had a slight lumbar scoliosis to the left, with some limitation of motion of the spine and tilting of the left hip.

Laboratory examination revealed calcium 13.9 to 16.0 mg. and phosphorus 2.5 to 2.9 mg. per 100 cc. Alkaline phosphatase was 8.2 to 15.3 Bodansky units. Several urine specimens gave strongly positive reactions with Sulkowitch's reagent.

A spinogram was normal. A roentgenogram of the chest showed an S-shaped scoliosis of the thoracic portion of the spine. A roentgenogram of the lumbosacral part of the spine revealed scoliosis, transitional vertebra with bilateral pseudarthrosis, epiphysitis of the first and second lumbar vertebrae, and generalized coarsening of all bones. Roentgenograms of the skull showed osteoporosis, and those of the humeri and femora disclosed generalized osteoporosis, with some coarsening of the trabeculae. Cysts were not noted, and the lamina dura was present. Intravenous pyelograms were normal.

At operation an oval, yellow-brown adenoma in the region of the right inferior pole of the thyroid gland was removed.

On the third postoperative day the patient was sullen and discourteous to the persons in the ward. Evidence of tetany was not present. Subsequently, delusions developed. At that time the blood calcium was 9.9 mg. per 100 cc. Intravenous administration of calcium gluconate did not produce improvement. Because his behavior became unmanageable, he was transferred to a mental hospital, where he remained for three months. During this period, blood calcium and phosphorus values were determined on numerous occasions. Most of them were normal, although they ranged from 5.9 to 12.5 mg. per 100 cc. for calcium and 3.2 to 4.5 mg. per 100 cc. for phosphorus. No correlation between his blood findings and his behavior was apparent. Electroencephalographic tracings were considered normal.

At the time of his discharge it was the opinion of his physician that the patient had had a postoperative reaction, partly determined by a metabolic abnormality and an "abnormally vulnerable personality structure."

The patient's course was followed for two years after his discharge from the mental hospital, and when last seen he was physically well and without psychic symptoms. However, a tendency to be erratic in his behavior and somewhat undependable at his work was apparent.[9]

Bone Disease; Renal Calculi; Renal Insufficiency, with Good Result.—CASE 12.—A 53-year-old woman complained of knee pain of three years' duration. Her past history revealed an episode of right ureteral colic three years previously, followed by passage of a stone. Systemic and urinary symptoms were not present at the time of examination.

Physical examination revealed a moderate degree of dorsal kyphosis and outward bowing of both thighs. The blood pressure was 200 mm. systolic and 100 mm. diastolic.

The findings on laboratory examination were as follows: hemoglobin, 10.4 gm.; total blood protein, 6.3 gm.; albumin, 4.2 gm.; globulin, 2.1 gm.; nonprotein nitrogen, 70 mg.; calcium, 14.4 mg., and phosphorus, 3.6 mg., per 100 cc. Alkaline phosphatase measured 46.0 Bodansky units. Phenolsulfonphthalein excretion was 35% in one hour.

Roentgenographic examination of the knees revealed osteoporosis with cysts in the lower femur on the right; of the pelvis, complete absorption of the descending ramus of the right pubis and multiple cysts, and of the chest, multiple cysts in ribs. Retrograde pyelograms disclosed a large calculus in the left kidney. Intravenous pyelograms showed diminished excretion bilaterally.

On exploration of the neck, an adenoma was found in the region of the left inferior lobe of the thyroid and was excised.

Postoperatively, tetany of moderate severity developed which was controlled by intravenously and orally administered calcium and dihydrotachysterol.

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9. Dr. Louis E. Reik, Assistant Superintendent, Butler Hospital, Providence, R. I., made follow-up examinations on this patient.

The patient's course has been followed for four and one-half years, and throughout this period renal function has not improved. The blood nonprotein nitrogen has varied from 58 to 105 mg. per 100 cc. Nevertheless, the patient has felt exceedingly well.

Bone Disease Without Renal Calculi; Giant-Cell Tumor.—CASE 19.—A 34-year-old white woman came to the clinic because of complaints of severe pain in the knees, legs, feet, arms, and back and profound muscular weakness which had become progressively severe during the previous three years. Determinations of the blood calcium, phosphorus, and alkaline phosphatase levels on two previous occasions had been reported as normal. A biopsy specimen of a lesion in the right tibia had been reported as "giant-cell tumor."

Physical examination showed marked bone tenderness, particularly on palpation of the tibiae, and extremely severe muscular weakness.

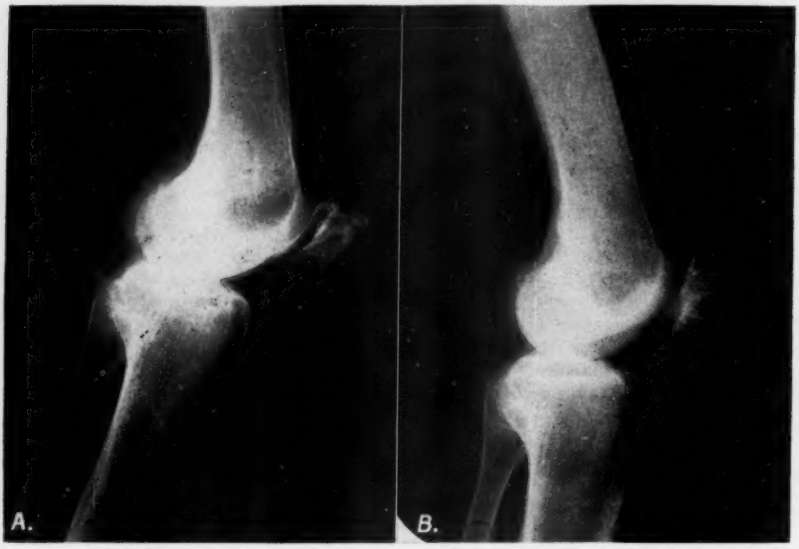

Fig. 2 (Case 19).—*A*, left patella before operation. *B*, left patella two and one-half years after operation.

The results of laboratory examinations were as follows: nonprotein nitrogen, 28 mg.; calcium, 14.4 mg.; phosphorus, 2.4 mg., and total protein, 6.3 gm. (albumin, 3.9 gm.; globulin, 2.4 gm.), per 100 cc.; alkaline phosphatase was 8.2 Bodansky units.

Roentgenographic examination of the skull showed decalcification with the table markings poorly differentiated and some absorption about the roots of the left upper incisor and left central and lateral incisors, with absent lamina dura; examination of the pelvis disclosed decalcification of bones of the pelvis and femora, with one cystic area in the left ilium; that of the knees, a large cystic lesion in the superior portion of the left patella and right upper tibia with generalized decalcification, and that of the ribs, decalcification.

At operation a smooth, orange-brown, opaque adenoma was found on the inferior aspect of the right lobe of the thyroid gland.

Postoperatively, there was evidence of mild tetany, which was easily controlled. On the first postoperative day the blood calcium was 9.9 mg. and the phosphorus 2.0 mg. per 100 cc.

One and one-half years after operation the patient was in excellent health. Normal strength was regained, and symptoms were not present. Two and one-half years later, she was in excellent health but had gained too much weight. Roentgenograms of the spine revealed coarsening

throughout the trabeculae. Valgus deformity of the hip was noted. There were ill-defined cystic areas in the left patella. Figure 2 shows roentgenograms of this patient's patella before and two and one-half years after operation.

Dental Problem: Multiple Operations; Partial Disappearance of Calculi.—CASE 16.—A 31-year-old woman had noted a swelling of the jaw one year previously. At that time a dental roentgenogram had revealed a cyst of the mandible. Four teeth were extracted, and the cystic area was curetted. She was then asymptomatic until three months before her visit to the clinic, when she again noted a growth on her jaw. Roentgenographic examination at that time revealed multiple cysts in the mandible and in the pubis. Renal calculi were noted on a roentgenogram of the kidney, ureter, and bladder. Blood studies showed an elevated calcium and a lowered phosphorus level. Exploration of the neck was done elsewhere, and "three glands" were said to have been removed. After the operation, the fluid intake was increased.

On her admission to the clinic, laboratory studies were done and revealed a total blood protein value of 6.8 gm.; a calcium value of 14.5 to 15.1 mg., and a phosphorus value of 1.8 to 3.9 mg., per 100 cc. Alkaline phosphatase measured 4.8 to 6.8 Bodansky units. Roentgenographic

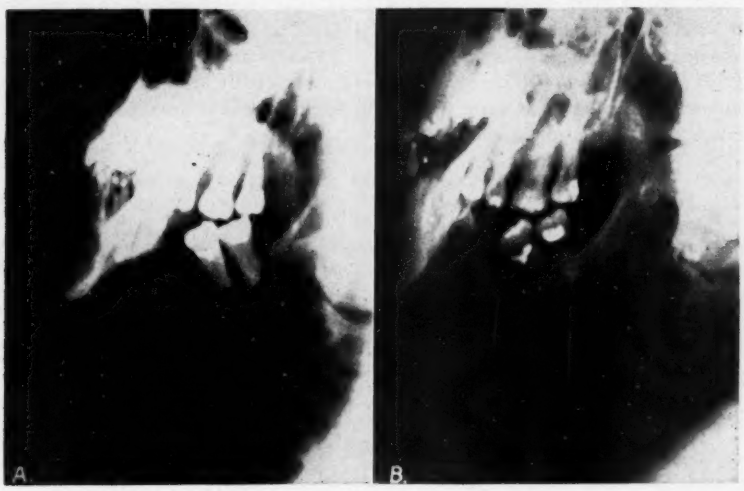

Fig. 3 (Case 16).—*A*, mandible before operation. *B*, mandible three years after operation.

studies showed multiple bone cysts and bilateral small renal calculi. The periodontal membrane was absent.

At a second exploration an adenoma was found at the inferior pole of the right lobe of the thyroid gland and was excised.

The postoperative course was uneventful, and tetany did not develop. The blood calcium, phosphorus, and alkaline phosphatase levels returned to normal.

Three years later the patient was in excellent health. Although some small areas of calcification were seen in the region of the lower pole of the left kidney, no stones were passed. A roentgenogram of the jaw revealed increased bone density on the right at the site of the previous cyst. Figure 3 shows roentgenograms of this patient's mandible before and three years after operation.

Primary Hyperplasia; Renal Calculi Without Bone Disease.—CASE 21.—A 37-year-old white man was seen because of frequent episodes during the previous five years of renal colic, dysuria, and hematuria, with stones being passed. For one month epigastric distress, gaseous distention, and easy fatigability had been noted.

Results of physical examination were normal. Laboratory examination revealed calcium 11.0 to 11.4 mg. and phosphorus 1.9 to 2.5 mg. per 100 cc. Alkaline phosphatase was 1.8 to 2.5 Bodansky units. Roentgenographic studies of the skull and chest disclosed a normal condition. The lamina dura was present. Intravenous pyelograms showed multiple, small, bilateral renal calculi.

At operation, four enlarged parathyroid glands were identified. The right inferior and left inferior glands were excised. Pathologic examination revealed hyperplasia involving chief cells primarily.

The postoperative course was uncomplicated. Tetany did not occur. On the first postoperative day, the blood calcium was 9.9 mg. and the phosphorus was 3.2 mg. per 100 cc. During the postoperative follow-up period of six months, the patient felt well, the blood calcium, phosphorus, and phosphatase levels remained normal, and he continued to pass stones. However, at the last examination a roentgenogram of the abdomen showed that most of the stones had disappeared. There was a question of a small calculus still visualized in the right kidney.

SUMMARY

Data on 25 cases of proved hyperparathyroidism are presented. The diagnosis was established by surgical removal in 24 cases and at autopsy in 1 case. The pathologic diagnosis was single adenoma in 24 cases and hyperplasia of the parathyroid glands in 1 case. There was no operative mortality. More than one exploration was required in four cases before the adenoma was discovered. Response to treatment was excellent in every case.

Case Reports

CRYPTOCOCCIC MENINGITIS OF NEARLY SIXTEEN YEARS' DURATION

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THE CLINICAL course of meningitis due to Cryptococcus neoformans (Torula histolytica) is usually one of steady progression to death within a few weeks or months. Occasionally, however, the disease may exhibit great chronicity, lasting for years. One patient lived five and a half years [1]; Reilly and Artman reported on a patient who was still living, though not wholly well, nine years after the onset.[2] Two instances of "recovery" have been reported,[3] but in neither of these was the spinal fluid normal at the time of the last observation.

Herewith is reported the case of a young woman who died of cryptococcic meningitis after an illness lasting nearly 16 years.

REPORT OF CASE

At the onset of her symptoms the patient was 18 years of age. In the latter part of June, 1935, she began to complain of severe headache, diplopia, and blurring of the vision. On Aug. 12, 1935, she was admitted to a hospital in Atlanta, where, after examination, a ventriculogram was done. This showed no dilatation of the ventricles and no evidence of tumor, but the ventricular fluid was found to contain 41 cells per cubic millimeter. On Oct. 10 a subtemporal decompression was performed. When the dura mater was incised, the arachnoid was noted to be studded with "tubercles." A tentative diagnosis of tuberculous meningitis was made, and the appearance on a subsequent histologic examination of a piece of the arachnoid tissue was interpreted as compatible with that diagnosis. After operation, however, the patient's condition improved gradually, so that she was able to be discharged from the hospital in November. By January, 1936, she was well enough to take a secretarial course and to be employed later as a secretary. In 1939 she married.

In December, 1941, she began having episodes of nausea, vomiting, constipation, headaches, and sensations of tightness in the lumbar region. It was necessary for her to stop working in February, 1942. During the first half of 1942, she was admitted to two hospitals, where various studies were carried out, but lumbar puncture was omitted. Tentative diagnoses of psychoneurosis and spastic colitis were made.

The patient was admitted to Grady Hospital for the first time on Sept. 6, 1942. Lumbar puncture revealed increased spinal fluid pressure and pleocytosis (Table). Cultures and guinea-pig inoculation for tuberculosis gave negative results. Her condition gradually improved without specific treatment, and she was discharged to be followed as an outpatient.

From the Department of Medicine, Emory University School of Medicine, and the Medical Service, Grady Memorial Hospital, Atlanta.

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On Dec. 7, 1942, lumbar puncture was done in the outpatient clinic. The fluid was inoculated into guinea pigs and cultured on Sabouraud's medium. One week later a yeast-like organism was found in the Sabouraud cultures. This was later injected into mice and found to be virulent in that animal, producing the typical histologic lesions of Cryptococcus infection. The cultures were sent to Dr. John F. Kessel, Los Angeles, who confirmed the identification as Cryptococcus neoformans. At this time the material removed for biopsy at her craniotomy in 1935 was reexamined, and yeast-like organisms morphologically compatible with Cryptococcus were recognized (Fig. 1). This established the fact that the original illness in 1935 had been cryptococcic meningitis instead of tuberculous meningitis and that the process was still active.

The patient was observed at intervals during the next nine years. She was readmitted Feb. 2, 1943, because of continuation of headache and drawing sensation in her back, and remained in the hospital until March 3, 1943, during which time she was treated with sulfathiazole and stibophen (fuadin®). A roentgenogram of the chest then showed a lesion resembling exudative tuberculosis in the right upper lung field. She had no cough but on request was able to produce a little sputum, which was found to be teeming with yeast forms. Cryptococcus neoformans was easily isolated from this sputum by culture. On April 28 a skin test was made, using 0.1

Summary of Results of Spinal Fluid Studies

Date	Cell Count, per Cu. Mm.	Polymorphonuclear Leucocytes, %	Protein, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.	Cryptococcus Culture
July 21, 1935	24	0	..	33	.....
Sept. 17, 1935	41	0	..	36	.....
Sept. 7, 1942	376	64	400	20	Negative
Sept. 28, 1942	151	75	80	..	Negative
Dec. 7, 1942	..	..	200	41	Positive
Jan. 4, 1943	85	15	..	..	Negative
Feb. 8, 1943	309	76	200	12	Positive
Feb. 24, 1943	222	72	400	21	Positive
Sept. 27, 1943	130	25	80	..	Positive
Oct. 20, 1944	71	0	149	..	Negative
Sept. 29, 1945	480	80	298	30	Positive
July 2, 1947	172	5	99	23	Positive
Sept. 17, 1948	63	95	109	27	Positive
Jan. 8, 1951	412	38	172	7	Positive

cc. of heat-killed suspension of her own organism; two days later the site of the skin test revealed a central area of bright erythema 5 by 3 mm., surrounded by a pale bluish-green area 1 by 1.5 cm. On the inner surface of the same arm and in the axilla were several areas of erythema and several vesicles. Five days later the patch of vesicles on the arm appeared typical of herpes zoster.

From May 11 to June 25 she was given a series of injections of Cryptococcus suspension subcutaneously, beginning with 0.1 cc. and increasing gradually to 1.0 cc. From June 25 to Aug. 20 she was given potassium iodide in increasing doses up to 40 drops three times a day. At this time all therapy was discontinued. She reported that she felt well and had no complaints of any kind. A chest roentgenogram showed resolution of the pulmonary infiltration noted in March.

On Sept. 24 she was found to be pregnant, and, because of the uncertainty of her future course, she was advised to have a therapeutic abortion. This was carried out between Oct. 5 and 15, without untoward event. On March 15, 1944, she reported that she was well and had again taken a secretarial job. On Oct. 20, 1944, she reported that she felt well, was still working, and had again become pregnant. She desired to go through with the pregnancy, and abortion was not advised. Nevertheless, a spontaneous miscarriage occurred on Nov. 30.

On Sept. 10, 1945, in response to a letter of inquiry, she reported that she felt well and was doing stenographic work. Her weight had gradually increased to 170 lb. (77.1 kg.), a gain of 50 lb. (22.7 kg.) over a three-year span. Spinal fluid examination was repeated, with the results shown in the Table. On March 1, 1946, she reported that she was feeling well and was pregnant for the third time. This pregnancy was completed successfully, with delivery of an infant at

full term on Oct. 25. In June of the following year she telephoned that she was fairly well but had some headache and a drawing sensation in her back from time to time. Her weight at that time was 180 lb. (81.6 kg.). Spinal fluid examination was repeated (Table).

On Sept. 17, 1948, she returned for a check-up. She had been taking care of her child and doing house work, but suffered from time to time from pain in the back and down the right leg and an occasional sensation of stiffness in the neck. Her weight was now 190 lb. (86.2 kg.). Lumbar puncture was difficult and very painful, possibly because of arachnoiditis. During the fall of 1948 she was given another course of autogenous vaccine injections three times a week, and therapy with potassium iodide was again tried. On Dec. 7, 1948, she reported that she felt well and attributed the improvement to the vaccine injections. However, in January, 1949, pains in her back and legs returned. In February she was readmitted to the hospital for study. A chest roentgenogram showed no evidence of pulmonary disease. She was given a trial course of sulfadiazine, 6 gm. per day, and a third course of vaccine injections. Lumbar puncture was not done because of the patient's fear of the procedure. The vaccine injections were continued on an outpatient basis until March 5, 1949, but no improvement ensued immediately. On May 25, however, she reported by telephone that she was feeling "fine."

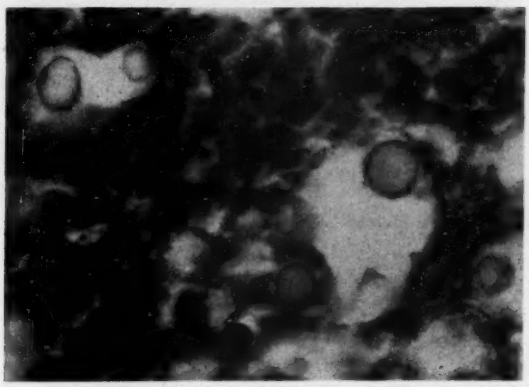

Fig. 1.—Tissue removed from meninges in 1935. Note typical yeast organisms surrounded by clear spaces representing capsular material. Aniline blue stain; × 660.

A telephone call on Jan. 10, 1950, disclosed that she was again pregnant and suffering from nausea and drawing pains in her back. Her second baby was delivered in August, 1950, without difficulty. She did not regain health after the delivery, however, complaining constantly of headache, weakness, and pains in the back of the legs. It was necessary for relatives to help with her house work and with the care of her two young children. In January, 1951, she was readmitted to the hospital for three weeks, during which she was given a course of prodigiosin, without improvement in her condition. On March 14, 1951, because of very severe headache and some vomiting, she was again admitted to the hospital. Examination disclosed nothing different from the findings on past admissions. The blood pressure was 130/85. Because of her severe headache and near mania, heavy sedation was induced with phenobarbital and codeine. Early on the morning of March 15, 1951, she asked for an enema. This was given and expelled satisfactorily, but 15 minutes later she was found dead.

Autopsy was performed four hours after death. The positive findings were limited to the brain, right lung, and left kidney. On avulsing the scalp, the defects of the right temporal decompression and the burr holes done 16 years previously were noted. There was some herniation of brain tissue covered by dura mater through all three openings. When the calvaria had been removed, the dura was noted to be so thin as to be almost transparent. It was only slightly adherent to the pia-arachnoid. The subarachnoid space was obliterated over the vertex of the brain. The gyri of the cerebrum were flattened, and the sulci were inconspicuous. On

removing the cerebrum, dense adhesions were observed at the base of the brain, particularly around the optic chiasm. When the tentorium cerebelli was incised, the cisterna magna was noted to be markedly distended with clear fluid. The foramina of Magendie and Luschka were obstructed by scar tissue, and the third ventricle was bulging downward. On puncture of the third ventricle, fluid escaped under pressure. There was a fine film of grayish-white opaque tissue occupying the subarachnoid space over the base of the brain. The middle cranial fossa was deepened and broadened, and there were flattening of the clinoid processes and widening of the sella turcica.

Dense adhesions were seen over the surface of the upper lobe of the right lung, and in its substance several scarred and calcified discrete nodular areas were noted. These averaged 3 mm. in diameter.

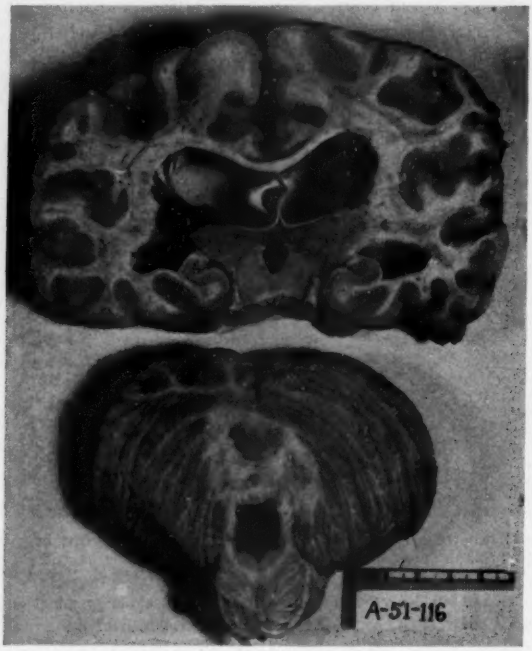

Fig. 2.—Coronal sections through cerebrum and cerebellum. All four ventricles are markedly dilated.

In the lower pole of the left kidney there was a yellow circumscribed area measuring 1.0 by 0.7 cm.

Examination of the brain after fixation showed it to be symmetrical. Transverse sections revealed marked dilation of all ventricles and the great cisterns (Fig. 2). In the region of the basal ganglia several small spongy areas were noted.

Histologic examination of the brain revealed the subarachnoid space to be obliterated in most areas by fibrous adhesions without appreciable inflammatory-cell infiltration. Sections through the basal ganglia showed small cystic areas of old encephalomalacia with slight gliosis. In these areas rare budding yeast-like bodies were identified. None of these was noted in the meninges. Histologic examination of the nodular areas in the lung and kidney showed calcified and fibrotic scars in which a few yeast-like organisms could be seen.

Cultures were made of meninges and the lung at autopsy, but, for reasons which are not obvious, no growth of Cryptococcus was obtained.

SUMMARY

A case is reported of chronic cryptococcic meningitis of nearly 16 years' duration. The diagnosis was established initially by craniotomy and on biopsy of a meningeal tubercle. Organisms were recovered from the spinal fluid on numerous occasions during the last eight years of her life. During that time spinal fluid examinations always revealed increased protein content, pleocytosis, and low sugar level. During most of the 16-year period the patient was relatively well, being able to do secretarial work, marry, and bear two children. At one time during the illness pulmonary cryptococcosis developed but regressed spontaneously after a few months. Various forms of therapy were given during the illness, but it could not be concluded that any of them affected the course of the disease.

In view of the great chronicity and tendency to spontaneous remissions exhibited in this case and several other cases, caution should be exercised in accepting reports of "recovery" in patients with cryptococcic meningitis.

UREMIA AND DISSEMINATED PLATELET-CELL (THROMBOCYTE) THROMBOSIS

Report of a Case Due to Malignant Nephrosclerosis with Acute Pancreatitis

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AND
ABE OYAMADA, M.D.
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THE CASE described in this study presents several unusual features: 1. No other case of clinical uremia due to malignant nephrosclerosis, acute pancreatitis, and proved platelet-cell thrombosis appears in the literature. There has been one somewhat similar case without platelet-cell thrombosis reported by Gambill.[1] 2. The entity, platelet-cell thrombosis, verified at necropsy, has been reported in only about 25 cases, and in only 2 cases was the diagnosis made or suspected ante mortem.[2]

In the case to be presented, the diagnosis of platelet-cell thrombosis was made post mortem.

Historically, the subject of pancreatic function and pancreatitis has been aptly recorded by many authors and requires little discussion here.[3] In brief, acute

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pancreatitis was first described as a clinical entity by Fitz in 1889. Claude Bernard suggested that the cause was autodigestion due to the activation of the pancreatic enzymatic secretions. This is reflected in our present use of the serum amylase and lipase activity and the secretin test in diagnosis.[3b', d'] All seem to conclude that in acute and chronic relapsing types of pancreatitis the serum amylase and/or serum lipase level is the single most reliable diagnostic feature and is considered pathognomonic,[4] Opie and Archibald (cited by Morton [3c']) demonstrated the part played by biliary tract infection. Langerhans (cited by Gambill and others [3z]) in 1890 called attention to the increase in calcium in the areas of fat necrosis of pancreatitis. These changes are due to the deposition of calcium soaps formed when fatty acids are liberated by the action of pancreatic lipase on neutral fat. This fact has since been utilized as an aid to clinical diagnosis since the changes are seen clinically as a decrease in serum calcium.[3w, x] Comfort and co-workers,[5] as recently as 1946, described the clinical picture of chronic relapsing pancreatitis with acute exacerbations of pancreatic inflammation, each attack adding an increment in residual pancreatic parenchymal damage and finally giving clinical evidence of pancreatic insufficiency. Insular deficiency appears at a late stage of the disease, when sufficient islets have been destroyed to impair carbohydrate tolerance and produce diabetes.

Hyperglycemia and/or glycosuria may be transient during attacks or persistent between attacks.[6] This has led Gambill to state that a diagnosis of chronic relapsing pancreatitis can be made in the presence of a combination of recurrent attacks of

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4. Footnote 3 *t*, *v*, and *d'*. Rich, A. R.: Role of Hypersensitivity in Periarteritis Nodosa as Indicated by 7 Cases Developing During Serum Sickness and Sulfonamide Therapy, Bull. Johns Hopkins Hosp. **71**:123, 1942.

5. Comfort, M. W.; Gambill, E. E., and Baggenstoss, A. H.: Chronic Relapsing Pancreatitis, Gastroenterology **6**:239 and 376, 1946.

6. Gambill.[1] King.[3a'] Comfort and others.[5]

severe upper abdominal pain plus diabetes, especially if the diabetes is known to have developed during the course of one of the acute attacks and there is no previous history of diabetes.[1]

Platelet-cell thrombosis is a comparatively recent entity. The pathologic lesions of the first case were described by Moschcowitz.[7] The cases reported since then have shown no particular predilection for white females or males and have involved both sexes in Negro patients.[8] Anemia and thrombocytopenia, obvious at the onset or developing rapidly and usually becoming severe, are noted. They are independent of any manifestations of bleeding. A leukemoid reaction may be seen. Hemorrhagic manifestations may or may not be noticed, but microscopic hematuria is almost always present. Neurologic disturbances of almost any conceivable type occur late in the disease.[9] These neurologic manifestations are bizarre and fluctuating and are the most distinctive clinical feature in these cases.

The lesions are most numerous in the myocardium, renal cortex, adrenal glands, and pancreas. An unquestioned diagnosis can be established at present only by demonstration of the characteristic lesion in the blood vessels of thrombi composed almost exclusively of thrombocytes (platelets).

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7. Moschcowitz, E.: An Acute Febrile Pleiochromic Anemia with Hyaline Thrombosis of the Terminal Arterioles and Capillaries: An Undescribed Disease, Arch. Int. Med. **36**:89 (July) 1925.

8. (*a*) Altschule, M. D.: A Rare Type of Acute Thrombocytopenic Purpura: Widespread Formation of Platelet Thrombi in Capillaries, New England J. Med. **227**:477, 1942. (*b*) Baehr, G.; Klemperer, P., and Schifrin, A.: An Acute Febrile Anemia and Thrombocytopenic Purpura with Diffuse Platelet Thromboses of Capillaries and Arterioles, Tr. A. Am. Physicians **51**:43, 1936. (*c*) Bernheim, A. I.: Widespread Capillary and Arteriolar Platelet Thrombi, J. Mt. Sinai Hosp. **10**:287, 1943-1944. (*d*) Brown, E. B., and Norman, J. W.: Multiple Platelet Thrombi, Clinical-Pathologic Conferences, New York J. Med. **46**:2167, 1946. (*e*) Carter, J. R.: Generalized Capillary and Arteriolar Platelet Thrombosis, Am. J. M. Sc. **213**:585, 1947. (*f*) Clough.[2a] (*g*) Engel.[2b] (*h*) Fitzgerald, P. J.; Auerbach, O., and Frame, E.: Thrombocytopenic Acroangiothrombosis (Platelet Thrombosis of the Capillaries, Arterioles, and Venules), Blood **2**:519, 1947. (*i*) Friedberg, C. K.; Gross, L., and Wallach, K.: Nonbacterial Thrombotic Endocarditis Associated with Prolonged Fever, Arthritis, Inflammation of Serous Membranes and Widespread Vascular Lesions, Arch. Int. Med. **55**:662 (Oct.) 1936. (*j*) Gitlow, S., and Goldmark, C.: Generalized Capillary and Arteriolar Thrombosis, Ann. Int. Med. **13**:1046, 1939. (*k*) Goldenberg, P. T.; Thayer, J. E., and Hastings, L. P.: Febrile Thrombocytopenic Purpura with Hemolytic Anemia and Platelet Thrombosis, New England J. Med. **243**:252, 1950. (*l*) Gore, I.: Disseminated Arteriolar and Capillary Platelet Thrombosis: Morphologic Study of Its Histogenesis, Am. J. Path. **26**:155, 1950. (*m*) Green, M. A., and Rosenthal, S.: Generalized Blood Platelet Thrombosis: Report of 3 Cases with Necropsy Findings, J. Mt. Sinai Hosp. **16**:110, 1949. (*n*) Muirhead, E. E.; Crass, G., and Hill, J. M.: Diffuse Platelet Thrombosis with Thrombocytopenia and Hemolytic Anemia (Thrombotic Thrombocytopenic Purpura), Am. J. Clin. Path. **18**:523, 1948. (*o*) Shwartzman, G.; Klemperer, P., and Gerber, I. E.: The Phenomenon of Local Tissue Reactivity to Bacterial Filtrates: The Rôle of Altered Vascular Response in Certain Human Diseases, J. A. M. A. **107**:1946 (Dec. 12) 1936. (*p*) Singer and others.[2c] (*q*) Singer, K.; Motulsky, A. G., and Shanberge, J. N.: Thrombotic Thrombocytopenic Purpura: Studies on the Hemolytic Syndrome in This Disease, Blood **5**:434, 1950. (*r*) Trobaugh, F. E., Jr.; Markowitz, M.; Davidson, C. S., and Crowley, W. F.: An Acute Febrile Illness Characterized by Thrombocytopenic Purpura, Hemolytic Anemia and Generalized Platelet Thrombosis, Arch. Path. **41**:327 (March) 1946.

9. (*a*) Fitzgerald and others.[8h] (*b*) Adams, R. D.; Cammermeyer, J., and Fitzgerald, P. J.: The Neuropathological Aspects of Thrombocytic Acroangio-Thromboses: A Clinico-anatomical Study of Generalized Platelet Thrombosis, J. Neurol., Neurosurg. & Psychiat. **11**:27, 1948.

Pertinent to the description of the case to be presented is the fact that the acute symptoms may be preceded by a period of vague ill health,[10] and that the condition has been known to develop in patients with chronic diseases, such as arthritis,[8g] tuberculous enteritis,[81] and glomerulonephritis.[81, n]

CLINICAL HISTORY

A 61-year-old woman was first seen on Aug. 6, 1948, at home in coma and was immediately hospitalized. The previous history of the patient, obtained from her son, disclosed that she had been under the care of a physician for the past two years because of "an enlarged heart and high blood pressure." During the last year she had visited her physician once a week. In late February or early March, the patient displayed swelling about the eyes, cheeks, and lips, and

Laboratory Findings

Blood Chemical Values

Date	Time	Blood Sugar, Mg./100 Cc.	Blood Urea Nitrogen, Mg./100 Cc.	Nonprotein Nitrogen, Mg./100 Cc.	Creatinine, Mg./100 Cc.	CO_2 Combining Power, Vol. %	Serum Amylase, Mg./100 Cc.
8/6/48	5 p. m.	247	151	...	..	..	...
	6 p. m.	...	...	...	..	.	296
	10 p. m.	504	162	253	.	..	...
8/7/48	7 a. m.	97	...	...	.	28	...
	9 a. m.	...	...	...	..	..	47
	12 a. m.	91	...	...	..	..	...
8/8/48	5:30 p. m.	236	...	...	..	..	...
	11 p. m.	168	...	...	.	61	...
8/9/48	.....	53	140	...	..	..	...

Blood Counts

	Red Blood Cells	White Blood Cells	Hemoglobin, %	Color Index	Stab Cells, %	Segmented Cells, %	Eosinophiles, %	Lymphocytes, %	Monocytes, %
8/6/48	3,640,000	31,000	58.8	0.77	2	92	0	4	2
8/7/48	3,190,000	19,000	57.6	0.92	4	89	1	5	1

Urinalysis

	Reaction	Specific Gravity	W. B. C.	R. B. C.	Blood (Chemical Reaction)	Sugar	Epithelial Cells	Uric Acid Crystals	Albumin Reaction
8/6/48	Acid	1.010	0-15	0	0	0	Occasional	0	2+

Spinal Fluid

8/7/48	Sugar, 255 mg./100 cc. Chlorides, 706 mg./100 cc. Total protein, 60 mg./100 cc.	Gold curve, 000111 Wassermann reaction, negative

finally, in April, 1948, she was admitted to another hospital. The diagnosis at this time was given as "hypertensive heart disease with beginning decompensation" and chronic hypertrophic arthritis. No blood sugar determination was recorded. It is important to note that there was no evidence of glycosuria during her stay in the hospital. After a one-month stay, a diet and oral medicament were prescribed and she returned home apparently improved. She then received occasional hypodermic medication from time to time. What the medication consisted of is unknown. During the period from May, 1948, there were recurrent peculiar episodes compatible with early senile dementia. There was no history of any other illness or surgical treatment. Questions relative to a possible previous diagnosis of diabetes mellitus elicited a definite and complete denial.

Physical examination on Aug. 6, 1948, disclosed a general flaccidity. The temperature was 104 F., the blood pressure, 230/130, and the pulse rate, 120 per minute, weak, and "thready." The skin felt warm and dry. There was a marked anemic pallor to the skin but no cyanosis. The tongue was coated. The eyeballs were soft to palpation. The pupils were equal and reacted

10. Footnote 8 *b*, *h*, and *l*.

to light. Ophthalmoscopic examination disclosed multiple bilateral hemorrhages and "cotton-wool" exudates. There was a suggestion of papillary edema of the right fundus. The lungs were clear except for a few crepitant rales in the right lower lobe posteriorly. The heart appeared to be enlarged to the left on percussion, but it was difficult to determine definite cardiac borders or tones because of the rapidity of the respiratory rate. Palpation of the abdomen revealed no rigidity or muscle spasm, but, when the mid-epigastrium was examined manually, despite her comatose state, the patient repeatedly responded with a groan. The bowel sounds were audible. The liver edge was palpable about 2 fingerbreadths below the costal margin. The laboratory findings are given in the table.

Fig. 1.—Kidney: Area of hemorrhagic necrosis in the cortex, with infiltration of polymorphonuclear leucocytes. This was the result of necrotizing activities of malignant nephrosclerosis. × 200.

The essential findings of a high blood sugar, increased temperature, high leucocyte count with a marked shift to the left, a blood chemical pattern such as one would find in uremia, and an elevated serum amylase value, with a precipitous drop to below normal values in 24 hours, led to the consideration of a diagnosis of Kimmelstiel-Wilson syndrome (intercapillary glomerulosclerosis) or subacute glomerulonephritis associated with acute pancreatitis.

Treatment consisted of measures to correct the acidosis, "splint" pancreatic function, protect liver function, combat anemia, and prevent respiratory complications. Accordingly, penicillin and streptomycin, M/6 lactate solution and dextrose solution intravenously, regular insulin, and blood transfusions were given.

The patient's condition remained essentially unchanged; she continued a downward course, exhibited a urea frost, and died two days following her admission.

Results of Postmortem Examination.—The body was that of a frail 61-year-old white woman, with pallor of the skin. Numerous recent hematomas were observed over sites of venepunctures, but no definite petechiae were present in the skin or in the pleural, pericardial, endocardial, peritoneal, and gastrointestinal mucosal linings. A recent superficial hematoma, 2 by 1 cm., was present in the lower outer quadrant of the left breast.

Gross Pathologic Observations: The essential gross anatomic findings consisted of malignant nephrosclerosis of the kidneys, with hemorrhagic necrosis of the cortex; marked hyper-

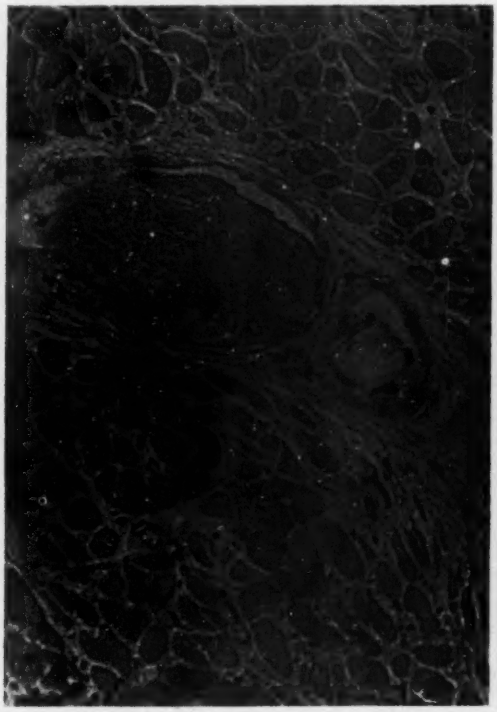

Fig. 2.—Heart: Platelet-cell thrombosis of small blood vessels in myocardium. Note homogeneous character of thrombi. In most of affected vessels seen, endothelium lining of the thrombus is smooth. × 200.

trophy of the heart, with focal acute myocardial infarction and mural thrombi in the right auricular appendage and left ventricle; bilateral bronchopneumonia and purulent bronchitis; slight arteriosclerosis of the aorta, and focal fat necrosis of the pancreas. The kidneys had a mottled outer surface, with alternating yellowish-gray and bright-red granular areas. On cut section, the architecture was disturbed, the cortex was narrowed, and numerous petechial hemorrhages were present in some parts of the pyramids. The spleen weighed 190 gm. and showed cyanotic induration. There were brown atrophy and fatty infiltration of the liver. The pancreas weighed 110 gm. and exhibited foci of fat necrosis. The adrenal glands presented nodular hyperplasia of the cortex.

Microscopic Pathologic Observations: On microscopic examination the kidneys (Fig. 1) revealed multiple cortical areas of hemorrhagic necrosis, with polymorphonuclear infiltrates in the interstitial connective tissue. Some medium-sized arteries were filled with recent thrombi; their walls were partly necrosed and were infiltrated with polymorphonuclear leucocytes. The wall of some arterioles had been replaced by pinkish homogeneous material.

Various sections of the heart revealed the small arterioles and capillaries to be filled with thrombi, rather homogeneous (Fig. 2). Some vessel walls showed definite necrosis in various places, with proliferation of the endothelium. Other small blood vessels presented older thrombi in the process of organization. The various thrombi will be analyzed in more detail in a later section of this presentation.

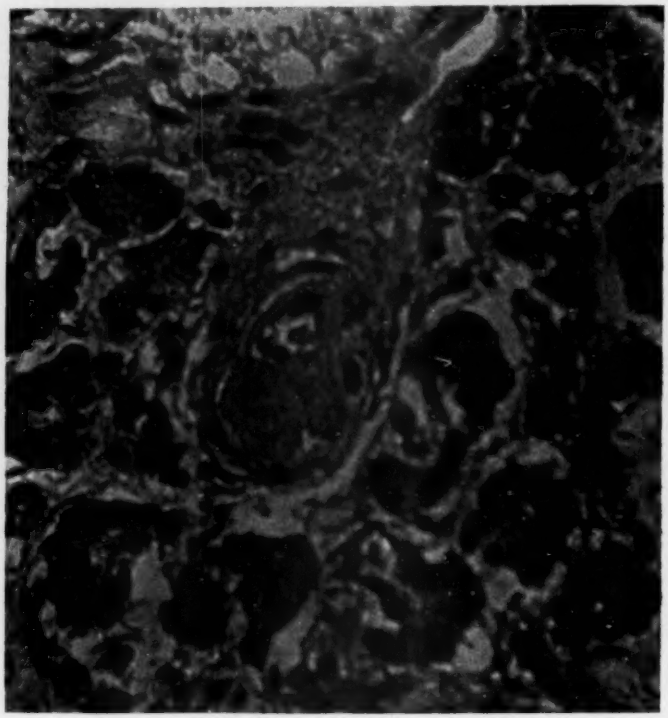

Fig. 3.—Pancreas: Platelet-cell thrombosis in arteriole. × 200.

The pancreas showed some edema and in the tail area a small focus of necrosis. The arterioles had markedly thickened walls, with some of the lumens being closed. Some blood vessels had focal lesions like those found in the myocardium (Fig. 3). Many of the fine secretory ducts of the pancreas were filled with inspissated material and were dilated, changes resembling those seen by Baggenstoss in ulcerative colitis and in uremia.[11]

There were focal necrotic changes in the liver (centrolobular). Megakaryocytes and platelet thrombi were not found in the pulmonary capillaries. Sections of bone marrow showed no changes.

11. Baggenstoss, A. H.: Dilatation of the Acini of the Pancreas: Incidence in Various Pathologic States, Arch. Path. **45**:463 (April) 1948. Ball, P., and Baggenstoss, A. H.: The Pancreas in Chronic Ulcerative Colitis, Proc. Staff Meet., Mayo Clin. **25**:256, 1950.

Vascular Lesions: The thrombi in the capillaries and arterioles of the heart and pancreas were investigated with the following special stains: Mallory trichrome, iron stain with Turnbull's blue (ferrous ferricyanide), and leuco-periodic acid (Schiff reaction), in addition to the usual hematoxylin and eosin stains. No thrombi were noted in the venules or in the larger arteries. The thrombi were homogeneous and in places granular (Fig. 4). Tinctorially, there was absence of hemoglobin. The Schiff periodic-staining reaction revealed nodular hyaline areas of the wall to take on a bright red hue on a yellowish background, thus corroborating the observations of Gore.[81] In what were regarded as "younger" lesions the endothelial lining about the thrombus was smooth and presented no proliferative activity (Fig. 4). In the older thrombi the enclosing endothelium showed evidence of proliferation (Fig. 5), often with admix-

Fig. 4.—Arteriole of myocardium: High magnification of platelet-cell thrombus, revealing texture of thrombus. In one area of vessel wall endothelial lining is absent and appears to be reflected upon surface of thrombus. This thrombus is regarded as a relatively "young" lesion. × 500.

ture in the thrombus of endothelial cells resembling fibroblasts. Therefore, the morphologic appearance of the thrombi in the small arterioles and capillaries corresponded closely to that previously described in disseminated capillary and arteriolar platelet thrombosis.

COMMENT

With two exceptions,[81] the clinical reports on disseminated arteriolar and capillary platelet thrombosis emphasize the presence of purpura or petechiae. In the case presented there were cutaneous hemorrhages, but only at the sites of attempted

venepuncture. No thrombocyte counts were done during life. However, reexamination of blood smears taken on two occasions showed an almost complete absence of thrombocytes and the presence of an occasional nucleated red blood cell. Thrombocytopenia in this condition is attributed to the withdrawal of thrombocytes from the circulation as the lesions of platelet-cell thrombosis are being formed. In spite of this lack of thrombocytes there were no hemorrhages. The hematuria could be accounted for by the necrotizing lesions in the glomerular tufts and renal pyramids without invoking thrombocytopenia. Singer, Bornstein, and Wile [2c] feel that a lack of thrombocytes per se does not necessarily result in purpura and that for bleeding

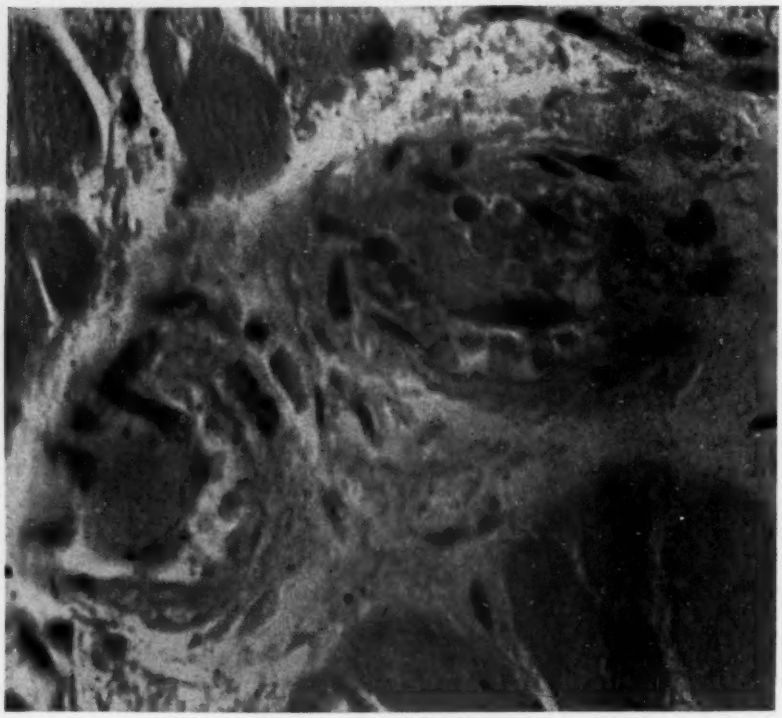

Fig. 5.—Arterioles of myocardium: High magnification of two blood vessels demonstrates proliferation of endothelial cells resembling fibroblasts in older lesions. × 500.

to occur the capillary endothelium must first be damaged, possibly by a "toxic" factor.[12] Hypersensitivity to sulfonamides [13] and iodine [14] has been reported, but in this case no drug sensitivity could be definitely proved. In this case only the myocardium and the pancreas were involved to any extent by platelet thrombosis,

12. (*a*) Shwartzman and others.[8o] (*b*) Shallow, T. A.; Eger, S. A., and Wagner, I. B.: Acute Pancreatitis, Postgrad. Med. **2**:288, 1947.

13. Engel and others.[2b] Polowe.[3d'] Fitzgerald and others.[5h]

14. Ehrich, E. W., and Seifter, J.: Thrombotic Thrombocytopenic Purpura Caused by Iodine, Arch. Path. **47**:446 (May) 1949.

so that the extent of involvement was perhaps not generalized enough to be manifest as hemorrhages in the skin and mucosa. Inasmuch as an abnormal condition of the blood was not suspected during life, no special studies were carried out for the hemolytic anemia often associated with this disorder. The absence of jaundice at autopsy would seem to point to a minimal, if any, hemolytic process. For the same reason no bone marrow studies were made during life, although in those cases in which suitable material has been studied no evidence of arrest of thrombocyte formation has been demonstrated.[15]

The predominant anatomicopathologic observations were those of anarteriolar and arterial necrosis of the kidneys, with acute necrotizing arteritis leading clinically to a uremic condition. An unexpected postmortem finding was the presence of platelet thrombi within the capillaries and arterioles of the heart and of the pancreas. Platelet thrombosis, as was previously stated, has never been reported in the presence of malignant nephrosclerosis and diabetic syndrome. The neurologic manifestations, such as coma, may well be explained on the basis of acidosis and uremia in the presence of uncontrolled diabetes, but in view of the many recent reports on the neuropathologic involvement of the small cerebral vessels in this syndrome, one might speculate on the possibility of platelet thrombosis in the cerebral capillaries as a partial explanation of the coma.[16] No postmortem study of the brain was permitted.

Little can be added in regard to the etiology and pathogenesis of disseminated arteriolar and capillary platelet thrombosis. Previous attempts at an adequate explanation for the vascular lesions have been along the line of a mechanism involving previous sensitization of the patient to an antigen, either chemical or bacterial, or of other origin.[17] A chemical hypersensitivity may be involved in our case, in view of the history of the injections of medicine a day or two before admission. Nothing can be stated about the priority of development of the lesions, i. e., whether thrombosis occurred first and endothelial proliferation later or vice versa.

SUMMARY

A case of platelet-cell (thrombocyte) thrombosis associated with uremia due to malignant nephrosclerosis, acute pancreatitis, and pancreatic insular insufficiency (diabetes) is presented. No other such case has been reported in the literature.

Mrs. Catherine Malone, M.T., gave technical assistance. Miss Carol Kerr, B.P.A., Mount Sinai Hospital, and Mr. Thomas Scanlon, B.P.A., Chicago Medical School, made the photographs.

15. Engel.[2b] Singer and others.[2c] Footnote 8 *l* and *m*.

16. Footnoe 8 *h* and *k*. Adams.[9b]

17. Dameshek.[8u] Shallow and others.[12b] Ehrich and Seifter.[14] Friedberg, C. K., and Gross, L.: Nonbacterial Thrombotic Endocarditis Associated with Acute Thrombocytopenic Purpura, Arch. Int. Med. **58**:641 (Oct.) 1936.

Progress in Internal Medicine

THE RATIONALE AND CLINICAL USE OF STEROID HORMONES IN CANCER

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HAVERSTRAW, N. Y.

(Concluded from Page 685)

D. Malignant Pelvic Growths

Next to carcinoma of the breast, uterine cancer ranks as the commonest malignant growth in females, since 23% of cancerous white women have the disease (Dorn). From birth to death the probability of a woman's having carcinoma of the uterus is 3.56% (Morris and Meigs). There are three to five times more cervical than endometrial (fundal, corpus) cancers (Nathanson, 1944*a*) and five living patients with the neoplasm for each patient who dies of uterine cancer (Ackerman and del Regato).

1. *Endometrial Cancer.*—About 0.5% of women over 40 years old acquire endometrial cancer (Dorn), and the incidence is rising (Speert, 1948). The primary hope for cure includes a combination of radium therapy and surgical measures, with a five-year survival rate of 55 to 75% in operable cancers and 35 to 40% in cancers treated with radium and x-rays alone (Hertig and Sommers; Meigs, 1945; Palmer and others; G. V. Smith). Therefore, prevention and palliation are important problems for consideration.

a. Experimental Studies: In experimental animals, fundal cancer is rarely found or produced, although endometrial hyperplasia is easily induced by the administration of estrogen (Loeb and others; Nathanson, 1944 *a*; H. C. Taylor, 1944). In guinea pigs, leiomyomas of the uterus with slight invasive properties have been observed after estrogen administration. These tumors were not autonomous, since they regressed after estrogen administration was halted and were prevented by simultaneous administration of progesterone, desoxycorticosterone, or testosterone (Endocrine-Cancer Conference; Lipschutz and others; Rakoff; H. C. Taylor, 1944). They were probably not analogous to human fibroids, since they did not develop in other species treated with estrogen (H. C. Taylor, 1944) and attempts to treat human leiomyomas with progesterone have been unsuccessful (Segaloff and others, 1949). After they had recovered from toxemia of pregnancy, rabbits were reported to show neoplastic changes in the fundus which could progress to cancer (H. S. N. Greene, 1941; H. S. N. Greene and Newton). The process involved a gradual transition from a cystic glandular and papillary stage to loss of glandular architecture, anaplasia, and metastases. The primary neoplastic focus appeared to be dependent upon systemic intrinsic factors present in the primary host but not in normal animals (H. S. N. Greene and Newton). These factors may be hormonal. Since the liver was damaged by toxemia in these animals, it

was postulated that estrogen may not be inactivated as in normal rabbits, and, therefore, the hepatic damage may be influential in the pathogenesis of the fundal cancer (Burrows, 1945; H. S. N. Greene, 1941). However, with complete development of the process, the dependence on intrinsic factors for further stimulation ceased and the growth became an autonomous cancer (H. S. N. Greene and Newton). It is possible that this final change was correlated with chromosome abnormalities found in endometrial adenocarcinoma but not in benign lesions (Hertig and Sommers). A fundal carcinoma was discovered in an aged female rat subjected to hormonal imbalance and continuous estrogen stimulation throughout the lifespan (Pfeiffer). Further animal experimental studies may yet reveal a definite association between hormones and endometrial cancer.

b. Human Studies: In human beings the prolonged, unopposed action of estrogen has been incriminated by several authors as a factor in the production of fundal carcinoma (Ayre; Fremont-Smith and others; Gusberg; Novak and Yui; C. L. Randall; Speert, 1949 *b*; Vass), but others do not agree (Geist and Salmon; Geist and others; H. O. Jones and Brewer; Zondek). A careful examination of the evidence is, therefore, essential, since prophylaxis or treatment of the disease may be feasible if a hormonal factor is involved. Certainly other factors may be acting in conjunction with hormones, since a genetic influence has been demonstrated in several families with a high familial incidence and early onset of the cancer (Kennaway and Kennaway). However, this may be a manifestation of an inherited hormonal carcinogenic environment, as mentioned in the section on breast cancer (Wood and Darling, and prophylactic hormonal therapy may be rationally used in selected cases in such a family.

The peak age for endometrial cancer is the early postmenopausal years, although the age range is 10 to 86 years(Palmer and others; Speert, 1948). Between 75 and 85% of the patients are over 50 years old, and 40 to 45% are over 60 years old (G. V. Smith; Speert, 1948). About 75% of women with fundal cancer acquire it within 15 years of cessation of the menses (C. L. Randall). It is known that estrogens may continue to be excreted after the menopause, even though cyclic menses cease. Their origin may be the ovary and the adrenal gland (R. T. Frank and others; Llusia; Nathanson and others, 1940; H. C. Taylor, 1944). Therefore, estrogens can continue to act, unopposed by progesterone, upon the postmenopausal endometrium. This may account for the relatively frequent occurrence of endometrial hyperplasia in women after the menopause (Rakoff) and possibly influences the evolution of corpus adenocarcinoma (Gusberg; C. L. Randall). Furthermore, this neoplasm is rarely seen in oophorectomized women (Hertig and Sommers; C. L. Randall; G. V. Smith). In those rare cases in which it may occur, estrogenic function could have been taken over by the adrenal gland.

Hormonal irregularities have been noted with increased frequency in women who later have endometrial cancer. Some authors believe that a late menopause is frequent in these women (Ackerman and del Regato; Crossen and Hobbs; Palmer and others; C. L. Randall), but others do not agree (Hertig and Sommers; Speert, 1948). However, it has been noted that postmenopausal flushes and senile atrophy of the external genitalia are not found in patients with corpus cancer (C. L. Randall), suggesting prolonged estrogenic activity. Furthermore, there is general agreement on the high incidence of infertility and the low parity of these patients (Hertig and Sommers; Palmer and others; Sommers and others; Speert, 1948,

1949*a* and *b;* H. C. Taylor, 1944, indicative of a long-standing endocrinopathy. Cervical polyps, squamous metaplasia of the cervix, and fibroids, possible evidences of estrogenic action, are seen with greater frequency in women with fundal carcinoma (Hertig and Sommers; Pierce and Slaughter; Speert, 1948, 1949*a*). Some authors believed that women who acquire endometrial carcinoma within the first four decades of life conform to a definite hormonal pattern characterized by prolonged, unopposed estrogenic activity (Hertig and Sommers; Speert, 1949*a*), but these findings were not noted in another series within the same age group (H. O. Jones and Brewer). Endometrial hyperplasia, a product of persistent estrogenic stimulation (Zondek), is believed by most authors to be a precancerous condition in some patients (Crossen and Hobbs; Gusberg; Hertig and Sommers; Novak and Yui; Panel on Tumors; C. L. Randall; Sommers and others; H. C. Taylor, 1944). However, others believe that they are not necessarily associated, since hyperplasia is common while cancer is relatively infrequent (H. O. Jones and Brewer). Nevertheless, the frequent close relation of the two lesions histologically, in which a graded progression from the former to the latter is noted, similar to that seen in rabbits (H. S. N. Greene and Newton), indicates a common factor in their evolution (Fremont-Smith and others; Gusberg; Ingraham and others; Novak and Yui; Rakoff; H. C. Taylor, 1944). Furthermore, enzyme studies reveal the activity of beta-glucuronidase, an enzyme which directly mirrors cellular proliferation and estrogenic activity on the endometrium, to be the same for benign as for malignant fundal lesions (Odell and Burt). Endometrial alkaline phosphatase, also regulated by estrogenic stimulation, is inversely related to the degree of anaplasia in carcinoma (American Association for Cancer Research, 1949). These investigations indicate that the most highly malignant carcinomas may be functionally independent of estrogen, as noted in rabbits (H. S. N. Greene and Newton), but still may respond to the growth-stimulating properties of the hormone.

Studies of ovarian lesions associated with endometrial carcinoma have also tended to indicate an estrogenic factor in cancer development. Granulosa-cell and theca-cell tumors in the postmenopausal patient are known to secrete estrogen (Hodgson and others; Meigs, 1945; Taylor, 1944; Novak and Yui) and are associated with the production of corpus cancer in 10 to 20% of the cases (Gusberg; Hertig and Sommers; Hodgson and others; Ingraham and others; Meigs, 1945; Rakoff). Other ovarian lesions, such as stromal hyperplasia, theca lutein cysts (Hertig and Sommers; G. V. Smith; Woll and others), and follicle cysts without a corpus luteum have also been observed with increased frequency, suggesting a hormonal imbalance that possibly involves the anterior pituitary, adrenal cortex, and ovary (Hertig and Sommers; Speert, 1949*a*). As noted previously, uterine and breast carcinomas are seen in the same patient more frequently than would be expected from chance alone (Hertig and Sommers; Hodgson and others; Speert, 1948; H. C. Taylor, 1931), as though a common etiological factor, such as estrogenic stimulation, is present.

Liver damage with poor estrogen inactivation has been incriminated in endometrial cancer of rabbits (H. S. N. Greene, 1940, 1941; H. S. N. Greene and Newton). Low vitamin B excretion levels with abnormally high endogenous estrogen levels were noted in 18 of 20 women with fundal cancer (Ayre and Bauld). Ayre and Bauld interpret this nutritional deficiency as a possible cause of hepatic impairment, with resultant accumulation of estrogen leading to growth stimulation of the

sex organs and eventual cancer. Furthermore, a relatively high incidence of obesity and diabetes has been noted in association with corpus cancer (Hertig and Sommers; Palmer and others; G. V. Smith; Speert, 1948). These metabolic disorders are known to be associated with fatty infiltration of the liver and decreased liver efficiency (Best and Taylor). Of possible significance is the metabolic alteration in the normal estrone-estriol relationship, whereby patients with fundal carcinoma were unable to convert estrone into estriol (Pincus and Graubard). This may implicate a defect in the estrogen metabolism of the liver as having a role in the tumorigenesis. In one series, the incidence of cirrhosis was five and a half times greater in women with endometrial cancer than in those without it (Speert, 1949*b*). However, in a recent study Hall and Sun could find no relationship between the diseases.

Finally, there have been several reports in which prolonged estrogen administration appeared to have an etiological role in the production of fundal carcinoma (Fremont-Smith and others; Gusberg; Hertig and Sommers; Vass). Speert (1948) believes that the increasing incidence of the disease is due in part to the widespread use of estrogens, although others do not agree (Geist and others; Zondek). Certainly, estrogens should be used cautiously, with intermittent dosage if at all, in women who seem predisposed to the development of uterine cancer. Such women include those with a genetic background of fundal carcinoma (Kennaway and Kennaway) and symptoms and tissue changes suggestive of estrogenic activity after the menopause (C. L. Randall; Vass).

c. Treatment: (1) Prophylactic Therapy: Hormones opposing continuous estrogenic stimulation of the endometrium might rationally be used in prophylaxis of precancerous or cancerous lesions. The rabbit studies of H. S. N. Greene and Newton revealed that the development of an autonomous cancer proceeds through reversible transitional stages. In human beings, a similar gradual evolution was noted (Hertig and Sommers). Cases were reported in which the diagnosis of adenocarcinoma was made on curettage after prolonged estrogen stimulation, with no evidence of cancer in the excised uterus after estrogen treatment had been discontinued (Fremont-Smith and others; Geist and others; Gemmell and Jeffcoate). Therefore, in the genetically or hormonally predisposed type of patient, prophylactic administration of progesterone or testosterone may be useful, after curettage has ruled out the possibility of malignant growth already being present. In young women, appropriate doses of progesterone may be useful for converting a continuously proliferative type endometrium into a cyclic type with normal menses (Seeger). In postmenopausal patients of this category, restoration of cyclic menses with progesterone therapy may be psychologically traumatic. Therefore, appropriate intermittent doses of testosterone may be of aid in preventing continuous estrogenic stimulation by inhibition of pituitary gonadotropins (C. R. Moore and Price) or by specific neutralization of estrogen at the end-organ. (Shorr and others). In addition, testosterone administration may retard the recurrence of a fundal carcinoma after operation (Abel).

(2) Palliation: Progesterone and testosterone therapy might rationally be tried in palliation of the disease because of their mechanisms of action mentioned in the section on prophylaxis (Abel). However, the progress of the autonomous cancer may not be greatly affected (American Association for Cancer Research, 1949;

H. S. N. Greene and Newton), although some growth processes may be slowed if they are still under estrogenic influence (Odell and Burt). Irradiation and surgical treatment are rightfully applied in the earlier cases in the hope of cure, but it is only in the far-advanced, inoperable, autonomous cancers that hormonal treatment is applicable with little objective response expected. The few clinical trials with testosterone seem to bear this out, since there was no regression of the cancer (Abel; Chaney and Greenblatt; Wyatt; 1948). The cases included two adenocarcinomas (Abel) one sarcoma (Chaney and Greenblatt), and one squamous-cell carcinoma (Wyatt, 1948). However, these few patients had temporary symptomatic improvement, with a sense of well-being and improved morale, a gain in weight and an improved appetite, and control of menopausal distress (Abel). The dosage used was 150 mg. per week of testosterone propionate, and all patients displayed signs of virilism (Wyatt, 1948). Perhaps a higher dose is indicated, since further control of symptoms and vaginal bleeding was obtained when the dose was doubled (Wyatt, 1948). Further studies are needed before proper evaluation of the symptomatic palliation can be made.

(3) Treatment of chorioepithelioma (choriocarcinoma): Uterine chorioepithelioma presents a somewhat different problem. This cancer is usually associated with an increased excretion of gonadotropin. Since the sex hormones inhibit the production of gonadotropin (Best and Taylor; C. R. Moore and Price; Zondek), they may have some influence upon the malignant growth. Accordingly, diethylstilbestrol treatment was attempted in one case and was associated with a regression in lung and vaginal metastases (Kullander). In addition, temporary symptomatic relief was obtained and a decrease in gonadotropin excretion was noted. No histological changes were seen in the vaginal metastases after treatment. It appeared as though the cancer developed tolerance to the estrogen; doses were increased progressively from 3 to 1,000 mg. per day with repeated remissions at progressively higher doses. The neoplasm of a second patient failed to respond to treatment, even though the gonadotropin level decreased. Since spontaneous regressions of this cancer are occasionally seen, no definitive conclusions can be drawn.

2. *Cancer of the Cervix.*—Surgical treatment in selected cases, and irradiation are the primary hopes for cure of cancer of the cervix. The five year survival rate varies with the extension of the disease, ranging from 50% in Stage I to 3% in Stage IV (Morris and Meigs). The problem of palliative therapy is, therefore, present in advanced cases.

a. Experimental Studies: Cervical cancer rarely develops spontaneously in experimental animals (Nathanson, 1944*a*; Panel on Tumors). However, estrogen administration produced squamous-cell carcinoma in mice of both high- and low-mammary-cancer strains; thus neither strain specificity nor the milk factor was essential (Allen and Gardner; Endocrine-Cancer Conference; Gardner, 1944; Gardner and others, 1938; Loeb and others; Pan and Gardner; Rakoff). These neoplasms were transplantable and autonomous (Endocrine-Cancer Conference). Progesterone or androgen administration did not prevent the appearance of the tumors (Pan and Gardner; Rakoff; H. C. Taylor, 1944), suggesting that a specific carcinogenic effect rather than a physiologic one may be involved. However, in other species estrogens have not produced malignant cervical growths, although squamous metaplasia of the cervix was often noted (Pfeiffer

and Allen; Rakoff; H. C. Taylor, 1944). Therefore, it appears that species susceptibility may be limited to mice in this respect.

b. Human Studies: The average age at recognition of the disease varies from 47 to 51 years, hinting at a relationship with the menopause (Ackerman and del Regato; Morris and Meigs; Nathanson, 1944*a*; Speert, 1948). However, no relationship could be established between the age at onset of the menopause and the age at cancer appearance (Morris and Meigs). The malignant growth arises more frequently in multiparous than in nulliparous women (Ackerman and del Regato; Morris and Meigs; Nathanson, 1944*a*; Rakoff; Speert, 1948; H. C. Taylor, 1944). Although birth trauma and resultant cervicitis are frequently given as causative factors for this increase, it may be significant that there are high levels of circulating hormones with hyperplastic cervical changes throughout the nine months of pregnancy (Rakoff; H. C. Taylor, 1944). Nevertheless, evidence for estrogenic factors in the evolution of human cervical cancer is only slight. A relatively large number of women with previous bilateral oophorectomy may acquire the disease, indicating that persistent estrogen stimulation is not essential to its evolution (Donnelly and Bauld; Morris and Meigs). Furthermore, the neoplasm has no predilection for occurring in association with other lesions of hyperestrogenism, such as granulosa-cell tumors and endometrial hyperplasia (Rakoff; H. C. Taylor, 1944). Estrogenic administration has been widespread for women of this age group, but few clinical reports have been published incriminating the hormone in the pathogenesis of the cancer (Gemmell and Jeffcoate; Nathanson, 1944*a*). Instead, squamous metaplasia and cervical erosions may be seen which regress after estrogenic treatment is halted (Geist and others; Rakoff; Zondek). However, Ayre believed that cervical cancer may be a local disordered growth response to cervicitis in the presence of estrogen excess and nutritional deficiency of thiamin and riboflavin. Furthermore, the activity of beta-glucuronidase, controlled by estrogen, is greater in the cancerous than in the noncancerous cervix (Odell and Burt). However, these women do not show evidences of hyperestrinism, and it has never been proved that there is an increased concentration of estrogen locally in chronic cervicitis (R. R. Green and Suckow). Furthermore, there was no selective absorption of radioactive diethylstilbestrol in the uterus of the mouse (Twombly and Schoenewaldt). Nevertheless, the concept of a local fixation of estrogen in the cervix, acting as a carcinogenic agent, offers the opportunity for prophylactic or therapeutic neutralization of its effect by testosterone.

c. Treatment: There have been two clinical attempts at the palliation of malignant cervical growths with testosterone propionate therapy, usually in doses of 150 mg. per week (Abel; Beecham). The results were similar to those obtained in treatment of fundal carcinoma. There was no objective regression or histological change in the cancer, but temporary symptomatic palliation was produced in almost all cases, including relief of pain (Abel; Beecham). Undoubtedly, the beneficial systemic effects of testosterone (Abels and others; Albright; Geist and others; Kenyon and others) were influential in producing the temporary subjective improvement. Since objective regression was not noted, it is doubtful whether a specific growth inhibition occurred.

3. *Ovarian Cancer.*—Ovarian carcinoma comprises only 15% of all pelvic cancers but ranks fourth among neoplasms responsible for death of women more than

40 years old because of its insidious onset and course (Ackerman and del Regato; Dorn). About 5,000 women die annually of this disease in the United States, and there are 2.8 living patients for each who die (Ackerman and del Regato; Dorn).

Only 20 to 25% of ovarian tumors are malignant (Ackerman and del Regato). Those tumors with cancer potentiality are papillary cystadenomas, solid tumor of the ovary, granulosa-cell tumor, teratoma, disgerminoma, arrhenoblastoma, adrenocortical tumor, and ovarian sarcoma. Rarely, a carcinoma may arise in an ovarian endometriosis (Ackerman and del Regato; Meigs, 1943; Novak). The prognosis of such cancers is usually poor, as demonstrated by the five-year survival rates of 21% for malignant papillary cystadenomas and 9% for solid carcinoma of the ovary (Meigs, 1943). Surgical measures and irradiation are the methods of treatment available at present, but steroid-hormone therapy may offer a means of prophylaxis or palliation in certain types.

a. Experimental Studies: In castrated mice, granulosa-cell tumors, luteomas (thecomas), and mixed-cell tumors have been produced by transplanting ovaries into the spleen or pancreas and thus causing a pituitary-gonadal endocrine imbalance (American Association for Cancer Research, 1949; Gardner, 1948; Li and Gardner). The increased production of F. S. H. in castrated animals is not inhibited because of the inactivation of estrogen in the liver before it enters the systemic circulation. Therefore, a prolonged hyperstimulation of the transplanted ovary occurs, suggesting the role of F. S. H. in the genesis of these tumors in mice. There is no strain specificity in this susceptibility in mice (Gardner, 1948; Li and Gardner). These tumors are transplantable and metastasize. Injections of estrogen and testosterone can prevent their formation, probably by inhibition of pituitary gonadotropin (Gardner, 1948; Li and Gardner). Irradiation of the ovaries in mice can produce similar transplantable tumors (Bali and Furth), possibly because of the impaired ovarian function after x-ray treatment (Gardner, 1948). It is not known whether such a hormonal imbalance may contribute to the genesis of these tumors in human beings.

b. Human Studies and Treatment: (1) Granulosa-cell tumors: Granulosa-cell tumors comprise 1.6% of ovarian neoplasms, and 10 to 25% are clinically malignant with recurrences and metastases (Hodgson and others; Meigs, 1943). These tumors are estrogen producers; endometrial carcinoma is associated in 10 to 20% (Hodgson and others; Ingraham and others; Rakoff) and breast carcinoma in about 5% (Hodgson and others). There is a relatively high incidence of infertility and menstrual irregularity in patients in whom granulosa-cell tumors develop (Hodgson and others). If the pathogenesis in human beings is similar to that in mice (Li and Gardner), intermittent doses of testosterone may be useful in preventing overstimulation of the ovary, with resultant tumors, in patients manifesting an abnormally excessive production of F. S. H. Furthermore, treatment of the hopelessly advanced tumor with testosterone may offer symptomatic relief, particularly from the effects of hyperestrogenism, as well as objective improvement (Abel; Novak). However, the latter is less probable, since the fully developed tumor appears to be autonomous of F. S. H., because the large amount of estrogen produced has no apparent effect upon halting the progress of the disease. Nevertheless, prophylactic use of testosterone may be of benefit postoperatively in lowering the recurrence rate of 5 to 28% or in delaying the onset of recurrences. Caution

in interpretation of results is necessary, since the appearance of spontaneous recurrences may be delayed 10 to 18 years (Novak). Progesterone therapy, theoretically, may be of aid in the same manner because of its inhibition of pituitary gonadotropin.

(2) Arrhenoblastomas: Arrhenoblastomas are occasionally malignant. The F. S. H. excretion is usually low, while the 17-ketosteroid excretion may or may not be elevated (Fraser and others; Meigs, 1943). These tumors produce defeminizing and masculinizing effects (Novak) because of androgen excretion. Estrogen administration may be of palliative benefit in reversing the symptoms of virilism in advanced cases. Since this tumor contains testicular elements, possible regression of the neoplasm may occur, as seen in testicular atrophy after estrogen administration for prostate carcinoma.

(3) Adrenocortical tumors: Adrenocortical tumors of the ovary may also become malignant and produce arrhenoblastoma-like symptoms and signs. There is usually an increase in 17-ketosteroid excretion in these cases because of the output of adrenal corticoid hormones by the tumor (Meigs, 1943; Novak). If these tumors are responsive to corticotropin therapy, then decreasing the output of the pituitary hormone by progesterone, testosterone, or adrenal cortical hormone administration may produce beneficial effects.

(4) Chorioepithelioma: Chorioepithelioma of the ovary, probably a type of teratoma, is occasionally very malignant. It is possible that estrogen administration will prove useful in the palliation of the far-advanced case as it has in a chorioepithelioma of the uterus (Kullander).

(5) Carcinoma in endometriosis: Rarely, carcinoma may develop in endometriosis. Testosterone administration may negate the influence of the ovary on endometriosis. Thus, intermittent androgen dosage may prevent the recurrence of the carcinoma or alter the course of a far-advanced, inoperable growth. Prophylactic use of testosterone in preventing the carcinoma is not rational because of the rare occurrence of the cancer, while endometriosis is relatively common.

(6) Disgerminoma: Disgerminoma is very malignant in the male (seminoma) but is only occasionally malignant in the female (Meigs, 1943). There are no endocrine changes associated with this tumor in the female (Novak). It is uncertain how endocrine alteration could affect this undifferentiated tumor, but there has been a report on a patient with multiple metastases in whom administration of testosterone propionate, 25 mg. per day, apparently improved the general health and prolonged the life. No objective effect on prevention or regression of metastases was noted (Russo and Kalso).

(7) Adenocarcinoma: Ovarian adenocarcinomas comprise the largest group of malignant ovarian growths (Ackerman and del Regato). Testosterone therapy has been tried in a few far-advanced cases with the hope of inhibiting the progress of the disease, possibly through action on the anterior lobe of the pituitary, since a direct effect on the ovary is not believed to occur (Abel; Chaney and Greenblatt; C. R. Moore and Price; Panel on Tumors; Wyatt, 1945). Temporary subjective improvement was noted in all 12 patients, with relief of pain (Beecham), gain in weight, strength, and appetite (Abel; Beecham; Chaney and Greenblatt; Wyatt, 1945), and possible prolongation of life (Abel; St. John). In one case, with a massive dosage of 300 mg. of testosterone propionate per day, the

pelvic mass decreased in size but there was no regression of liver metastases (St. John). The other patients had no objective evidence of cancer inhibition (Abel; Beecham; Chaney and Greenblatt; Wyatt, 1945). The temporary palliative benefits of steroid-hormone therapy in advanced cases of malignant pelvic growths (Tables 11 and 12) indicate the need for further trials in larger series of cases.

E. Lymphoma

Lymphoma is a general term for a group of diseases, neoplastic in character, including leukemias (lymphocytic, granulocytic [myelogenous], monocytic, eosino-

Table 11.—*Testosterone Treatment of Malignant Pelvic Growths*

Author	No. and Type of Cancer	Dosage	Symptomatic Improvement	Objective Improvement
Beecham	2-Cervical 4-Ovarian	30-175 mg./wk., intramuscularly	Good in 5	None
Abel	7-Cervical 2-Corpus 4-Ovarian	140-150 mg./wk. orally or intramuscularly	Good in all; life prolonged in some	None
Wyatt	1-Ovarian	600-750 mg. total in 8 wk.	Short	None
Chaney and Greenblatt	1-Corpus sarcoma 3-Ovarian	?	Short	None
Wyatt	1-Corpus	150 mg. then 300 mg./wk. (maintenance)	Good; prolonged life	None
St. John	1-Ovarian	300 mg./day	Good; prolonged life	Decreased size of pelvic mass
Russo and Kalso	1-disgerminoma	25 mg./day	Good; prolonged life	None

Table 12.—*Estrogen Treatment of Malignant Pelvic Growths*

Author	No. and Type of Cancer	Dosage	Symptomatic Improvement	Objective Improvement
Kullander	2-Uterine chorioepithelioma	1-diethylstilbestrol, 3 mg./day up to 1,000 mg./day, orally and intramuscularly	Good; prolonged life	Regression of lung and vaginal metastases
		1-diethylstilbestrol, 15,820 mg. in 24 days	None	None

philic), Hodgkin's disease, lymphosarcoma, plasma-cell (multiple) myeloma, mycosis fungoides, and several other forms (Ackerman and del Regato). The basic pathologic changes include an abnormal growth of the lymphoid or blood-forming organs. Although surgical treatment or irradiation can produce a cure in a few cases of local disease, most lymphomas are invariably fatal. The palliative benefits of irradiation and nonsteroid chemotherapy are often remarkable, but there is a great need for clarification of the hormonal effects in the genesis and the possible treatment of these diseases.

1. *Experimental Studies.*—Experimental research has been concerned with leukemia and lymphosarcoma in animals. The metabolism of mouse leukemia tissue qualitatively resembles that of cancerous tissue, but the deviation from normal is of less magnitude (Kirschbaum). The tumors act like true malignant growths, with multiple organ invasion, transplantability, and progression to death (Endo-

crine-Cancer Conference; Furth and others; Gardner, 1944; Kirschbaum). Lymphosarcoma and leukemia appear to be different morphological manifestations of the same fundamental disease (Kirschbaum). Mouse leukemia is similar to that seen in man (Kirschbaum).

a. Role of Heredity: Spontaneous lymphoid tumors and leukemias arose in some inbred strains of mice, implicating a genetic influence (Gardner and others, 1944; Kirschbaum; Law and Speirs). The leukemias were transplantable only by the inoculation of viable leukemic cells into a susceptible host, usually of close genetic background (Kirschbaum). The leukemic cells had different transplantation patterns that could be retained through many passages, suggesting an association between somatic mutation and cancer development (Furth and others). Furthermore, chromosomes of leukemic cells were noted to be larger than those of normal lymphocytes in long-transplanted mice leukemia (Biesele and Gasic), further supporting a chromosomal change in the evolution of the neoplasm.

b. Milk Factor: An influence in the milk of certain lactating female mice was found to be effective in promoting the growth of one myeloid and two lymphocytic leukemias in normally refractory mice (Law). This influence has the physical and chemical characteristics of a virus (Law) and may be a factor in the production of leukemia in mice (Law; Nathanson, 1944*a*).

c. Estrogen: A possible relation to endocrine balance was noted when castration increased the incidence of leukemia in males over that in females in some strains of mice (Law and others; McEndy and others; Murphy) and in fowls (Marine and Rosen, 1940). Ovariectomy produced varying results (Law and others; McEndy and others; Nathanson, 1944*a*). Injections of natural or synthetic estrogens increased the incidence of the lymphomas in some strains of mice and fowls (Endocrine-Cancer Conference; Gardner and others, 1944; Kirschbaum; Marine and Rosen, 1941; Murphy; Nathanson, 1944*a*). The induced estrogen imbalance may have been a factor in stimulating or activating the agents responsible for the lymphoblastic tissue growth (Marine and Rosen, 1941). Chromosome studies of mouse leukemia (Biesele and Gasic) revealed that leukemic cells in males were associated with chromosomes larger than those in females. Ovariectomized female mice had even smaller chromosomes than intact female hosts. Treatment with testosterone maintained the chromosomes in spayed leukemic females at the large size found in male hosts with or without testosterone administration (Biesele and Gasic). Prophylactic administration of testosterone was found to lower significantly the incidence of leukemia in mice (Gardner and others, 1944; Marine and Rosen, 1941; Nathanson, 1944*a*; Sprague). These observations supported the possibility of sex-hormone effects in mouse leukemia (Biesele and Gasic). However, mouse leukemia developed in both sexes, and forced breeding did not increase the incidence, showing that the influence of estrogen may be a relatively minor factor (Kirschbaum). Furthermore, testosterone was of no benefit in the treatment of several strains of leukemic mice (Burchenal and others).

d. Adrenal Cortex: The relationship of adrenal cortical function to leukemia in mice has produced the greatest strides in advancing a possible pathogenetic concept and treatment for the disease. There is an inverse relationship between the size of the lymphoid organs and adrenal cortical activity (Levin, *a*). Adrenalectomy of mice produced thymic hypertrophy and lymphoid hyperplasia and doubled the sus-

ceptibility to transplanted lymphatic leukemia (Law and others; Murphy and Sturm, 1943, 1944*b*). Conversely, administration of corticotropin or adrenal 11-oxycorticoids produced thymic and lymphoid tissue atrophy with lymphopenia (Dougherty and White, 1943, 1947; Panel on Lymphoblastomas; Sprague). Histological examination revealed degeneration and pyknosis of the lymph node cells (Panel on Lymphoblastomas). Administration of adrenal corticoids decreased the number of successful leukemic transplantations in some, but not in other strains (Dougherty and White, 1943, 1947; Murphy and Sturm, 1944*a*). No effect on the polymorphonuclear cells was noted (Dougherty and White, 1947). Corticotropin administration in adrenalectomized animals did not produce these effects, indicating that the adrenal corticoids were the active agents involved (Dougherty and White, 1947). Variable effects were obtained with desoxycorticosterone therapy in different strains (Dougherty and White, 1947; Murphy and Sturm, 1944*a*). The course of spontaneous (Law and Speirs) and transplanted lymphomas (Heilman and Kendall; Lewis and others; Sprague) was temporarily retarded by adrenal corticoid therapy in some strains but not in others (Levin, *a*). Nonspecific tissue damage also produced some temporary regression of lymphomas, apparently by increasing the output of the adrenal cortex (Bass and Feigelson). Tumors in female mice treated with cortisone regressed to a greater extent than those in male mice, while castration or estrogen treatment of the male mice enhanced the effect of the hormone (Heilman and Kendall). Estrogen treatment in mice was shown to enlarge the pituitary and adrenal glands (Burrows, 1936; Gardner and others, 1944), possibly by stimulating the production of corticotropin (Burrows, 1936, 1945), and, thus, may have its enhancing effect upon regression. It has been postulated that the increased incidence of lymphomas in estrogen-treated animals may be secondary to regression of lymphoid tissue, mediated through the adrenal gland, with a resultant occurrence of abnormal growth patterns (Gardner and others, 1944). A marked decrease in adrenal cholesterol was observed in mice with leukemia, which might indicate that an excessive secretion of cortical hormones was involved in the evolution of the neoplasm (Levin, *a*). The prophylactic value of testosterone could be explained by its inhibition of corticotropin. An alternate possibility is that a lack of cortical hormone, due to a specific block upon its production from cholesterol, may be involved in the excessive lymphoid production. The latter postulate is supported by the finding of subnormal levels of 17-ketosteroid excretion in five patients with lymphocytic leukemia (Levin, *a* and *b*). If decreased adrenocortical function is involved, then supplemental cortical hormone therapy might alleviate the disease (Levin, *a*).

2. *Human Studies.*—There is a familial incidence of 8 to 9% among patients with leukemia, indicating a possible genetic influence in the pathogenesis (Gross and Matte; Videbaek), as noted in mice (Gardner and others, 1944; Kirschbaum; Nathanson, 1944*a*). There is no evidence of a milk factor or of estrogenic stimulation as being active in human cases of leukemia (Nathanson, 1944*a*). However, there are suggestions that the adrenal cortex may participate in human (Dobriner and others, 1943, 1944, 1947; Levin, *a* and *b*; Panel on Lymphoblastomas) as well as in animal lymphatic lymphomas (Bass and Feigelson; Dougherty and White, 1943, 1947; Heilman and Kendall; Law and Speirs; Lewis and others). A deranged qualitative distribution in 17-ketosteroid excretion was demonstrated in lymphocytic but not in myeloid leukemia; an abnormal product, 11-hydroxy-etio-

cholanolone, was excreted in the former but not in the latter (Dobriner and others, 1944; Panel on Lymphoblastomas). Furthermore, markedly subnormal levels of 17-ketosteroids were found in five lymphocytic and allied leukemias, with normal levels in three myeloid leukemias (Levin, *a* and *b*). Since adrenal corticoids have a lytic action on lymphocytes and lymphoid tissue (Panel on Lymphoblastomas; Thorn and others) and temporary benefits have been produced in some animal lymphomas (Heilman and Kendall; Law and Speirs; Lewis and others), attempts to influence the course of the disease in human beings with adrenal corticoids were begun.

3. *Results of Treatment* (Table 13).—Corticotropin in doses of 20 to 60 mg. a day in children and 60 to 200 mg. a day in adults was used to stimulate adrenal cortical activity (Dameshek and others; Donohue and others; Pearson and others, 1949, 1950; Proceedings of First Clinical ACTH Conference; M. C. Rosenthal and others; Thorn and others). Results of cortisone therapy in doses of 50 to 600 mg. a day, with the usual dose being 150 to 300 mg. a day, were studied (Pearson and Eliel; M. C. Rosenthal and others; Schulman; Spies and others; S. G. Taylor and others, 1950; Thorn and others). A course of hormonal therapy usually extended for 18 to 32 days. In the leukemias, a complete remission includes both clinical and hematological improvement, whereas a partial remission implies that either feature may be lacking or slight. In the solid lymphomas the clinical improvement can be evaluated as good or fair.

The type of lymphoma that has been most frequently treated with hormones is the group of acute leukemias. In general, dramatic, complete remissions have been produced in 30 to 70% of these patients, with partial remissions in 10 to 20% (Blood Club; Cortisone Investigator; Dameshek and others; Pearson and Eliel; Proceedings of First Clinical ACTH Conference; M. C. Rosenthal and others; Schulman; Stickney and Watkins). Subjective improvement is manifested by an increase in appetite, weight, and strength with a feeling of well-being. These effects may be seen after two to three days of corticotropin and six days of cortisone therapy. Objective improvement is characterized by decrease in fever and bleeding episodes, a diminution in the size of enlarged lymph nodes, liver, and spleen, and healing of skin lesions. Furthermore, hematological improvement is often striking, with a marked decrease in blast forms in the peripheral blood and marrow and an increase in the reticulocytes, thrombocytes (platelets), erythrocytes, hemoglobin content, and mature leucocytes (Dameshek and others; Donohue and others; Pearson and Eliel; Pearson and others, 1949, 1950; Proceedings of First Clinical ACTH Conference; M. C. Rosenthal and others; Spies and others; Thorn and others). The acute lymphocytic leukemias may respond best (Dameshek and others; M. C. Rosenthal and others), but other authors have noted occasional improvement in patients with the acute granulosa-cell (myelogenous) form (Blood Club; Pearson and others, 1950; Schulman). Perhaps some of the disagreement is based upon the difficulty in differentiating the two forms in the acute blast stage (Blood Club). In addition, there is a lack of agreement whether adults with acute leukemia respond as often as do children (Blood Club; Dameshek and others; Pearson and Eliel; M. C. Rosenthal). Further studies on larger series and more varied age groups are necessary before a definite conclusion can be formulated on these points. Among 13 patients with acute monocytic leukemia, only 1 has had a remission

TABLE 13.—*Corticotropin (ACTH) and Cortisone Treatment of Lymphomas*

Reference	Lymphoma *	Dose	Results
Pearson and others, 1949	4 chronic LL 1 Ls 1 Hd	ACTH, 100-200 mg./day or cortisone, 200 mg./day	Partial remissions in all LL Good remission Good remission
Astwood and others	1 Mono L 1 subacute LL	ACTH, 30-80 mg./day	No response in Mono L Partial remission in LL
Blood Club (includes some previous reports)	124 acute L 7 chronic LL 6 Ls 6 Mono L 2 MM	Varied	Complete remission, 42; partial, 21 Partial remission in 6 LL Good remission, 2; fair, 1 No response in Mono L Good remission in 1 MM
Cortisone Investigator	25 acute L 10 Hd 6 MM	ACTH, 100 mg./day, or cortisone, 300 mg./day	Complete remission, 11; partial, 8 Good remission in 6 Hd Good remission in 4 MM
Cortisone Investigator; Donahue and others	1 eosinophilic L	ACTH, 40-80 mg./day	Complete remission
Dameshek and others	Acute and subacute 6 LL 2 ML	ACTH, 20-40 mg./day in children, 80 mg./day in adults	Complete remissions in 5 LL No response in ML
Kinsell and others	1 Mono L	ACTH, 60-100 mg./day	Complete remission
Pearson and Eliel	30 acute L 6 Ls 8 chronic LL 6 Hd 1 MM 4 ML 4 Mono L	ACTH, 50-200 mg./day, or cortisone, 100-400 mg./day	Complete remission, 13; partial, 9 Good remission, 2; fair, 4 Partial remission in 5 LL Fair remission in 4 Hd Good remission in MM No response in ML No response in Mono L
Pearson and others, 1950	4 acute ML 1 acute LL 2 acute LL	ACTH, 50 mg./day in children; 100 mg./day in adults Cortisone ? dose	Complete remission in all cases with either hormone
Proceedings of First Clinical ACTH Conference (Schwachman; Farber; Taylor and Morris; Bonner)	2 acute LL 1 acute L 1 mycosis fungoides 1 Hd	ACTH, ? dose ACTH, 50 mg./day ACTH, 100 mg./day ACTH, 50 mg./day	Complete remission Complete remission Clinical improvement and healing of skin lesions Slight improvement
Schulman	6 acute LL 1 acute ML 1 Mono L 1 ML	ACTH, 40-60 mg./day, or cortisone, 100-300 mg./day	Complete remission in 4 LL Complete remission No response No response
Spies and others	1 ML 2 chronic LL 1 acute L 2 Ls	ACTH, 100-160 mg./day, or cortisone, 150 mg./day	Partial remission Partial remissions in both LL Complete remission Good remission in both Ls
Stickney and Watkins	18 acute L 3 chronic LL 3 Hd	ACTH, 200 mg./day or cortisone, 200-300 mg./day; children, 50-75% of adult dose	Complete remission, 3; partial, 2 Partial remissions in all LL Good remission in all Hd
S. G. Taylor and others, 1950	2 acute ML 1 chronic LL 1 MM 3 Hd 6 Ls 2 mycosis fungoides	ACTH, 100-200 mg./day, or cortisone, 100-300 mg./day	No response in ML Partial remission No response Good remission, 2; fair, 1 Good remission, 2; fair, 4 Good remission, 1; fair, 1
Thorn and others	1 MM	ACTH, 80 mg./day	Good remission
Bell and Thomson	4 acute L 1 Mono L	Cortisone, 50-600 mg./day	Complete remission in 1 L only No response of Mono L
Earle and Reilly	4 LL (acute)	ACTH, 40-60 mg./day	Complete remissions in all
M. C. Rosenthal and others	13 acute LL 5 acute ML 2 Mono L 5 chronic LL 5 Ls 5 Hd 5 MM	ACTH, 40-80 mg./day, or cortisone, 100-150 mg./day and oral maintenance	Complete remissions in 9 Partial remission in 1 ML No response Partial remissions in 4 Good remissions in all Ls Good remissions in 3 Hd Good remission in 1 MM
Weder and Becker	3 LL 1 ML	Cortisone, 50-200 mg./day	No response No response

* LL indicates lymphatic leukemia; ML, myelocytic leukemia; L, leukemia; Ls, lymphosarcoma; Hd, Hodgkin's disease; MM, multiple myeloma, and Mono L, acute monocytic leukemia.

(Kinsell and others); therefore, it is generally agreed that hormonal therapy is of little value in this type (Astwood and others; Bell and Thomson; Blood Club; Pearson and Eliel; M. C. Rosenthal and others; Schulman). A patient with the rare acute eosinophilic leukemia was treated with corticotropin and had complete remission lasting 13 weeks and then one of another 6 weeks on re-treatment (Blood Club; Donohue and others). This beneficial result might be expected, since the effects of corticotropin and cortisone in producing eosinopenia are known (Sprague; Thorn and others).

Among the chronic leukemias, similar clinical remissions have been produced in most of the patients with lymphocytic leukemia (Blood Club; Earle and others; Pearson and Eliel; Pearson and others, 1949; M. C. Rosenthal and others; Spies and others; Stickney and Watkins). However, hematological improvement (Spies and others) was usually not noted (Pearson and Eliel; M. C. Rosenthal and others; Saunders and Adams; Stickney and Watkins; S. G. Taylor and others, 1950), despite the known effects of lymphopenia induction in nonleukemic persons (Saunders and Adams). One explanation offered was that an insignificant decrease in the circulating lymphocytes in a person with chronic leukemia might actually involve a great percentage change in the presence of a normal blood count (Saunders and Adams). Another factor might be a difference in the leukemic lymphocyte itself, making it more resistant to destruction by hormonal therapy. Nevertheless, some increase in the red blood cell and thrombocyte counts is frequently observed and is of benefit to the patient (Pearson and Eliel; Pearson and others, 1949; M. C. Rosenthal and others; Spies and others), particularly after therapy with myelosuppressive drugs has caused aplasia of the marrow. Chronic myelocytic leukemia rarely responds to corticotropin or cortisone therapy, but the number of patients treated is still small (Dameshek and others; Pearson and Eliel; M. C. Rosenthal and others; Spies and others; Stickney and Watkins; Weder and Becker). Theoretically, it may not be expected to improve, since myelocytic leukemia appears to be a different disease from lymphocytic leukemia, with differing adrenal cortical excretion products (Dobriner and others, 1944; Panel on Lymphoblastomas). Furthermore, neutrophiles are often increased after corticotropin or cortisone administration (M. C. Rosenthal and others; Thorn and others).

Good clinical remissions have been obtained in 16 and fair remissions in 5 of 29 patients with Hodgkin's disease (Cortisone Investigator; Pearson and Eliel; Pearson and others, 1949; Proceedings of First Clinical ACTH Conference; M. C. Rosenthal and others; Stickney and Watkins; S. G. Taylor and others, 1950). Good remissions have been noted in 15 and fair remissions in 8 of a total of 26 patients with lymphosarcoma (Blood Club; Pearson and Eliel; Pearson and others, 1949; M. C. Rosenthal and others; Spies and others; S. G. Taylor and others, 1950). In addition, several patients with acquired hemolytic anemia secondary to their lymphoma, had a marked hematological response with a decrease in the circulating hemolytic antibody (M. C. Rosenthal and others). Although most of these cases revealed a marked shrinkage of involved lymph nodes, spleen, and liver, some patients died during therapy or had exacerbations immediately on halting treatment. Therefore, they could not be included in the group with good remissions.

Eight of 16 patients with plasma-cell (multiple) myeloma exhibited subjective and objective improvement with hormonal therapy (Blood Club; Cortisone Investigator; Pearson and Eliel; M. C. Rosenthal and others; S. G. Taylor and others,

1950; Thorn and others). There was a definite decrease in marrow myeloma cells and serum globulin in some cases (Blood Club; Cortisone Investigator; Thorn and others) but not in others (Pearson and Eliel; M. C. Rosenthal and others; S. G. Taylor and others, 1950).

Two patients with mycosis fungoides were treated, with a pronounced healing of skin lesions in one (Proceedings of First Clinical ACTH Conference; S. G. Taylor and others, 1950).

Remissions may last one week to several months (Blood Club; Cortisone Investigator; Donohue and others; Pearson and Eliel; M. C. Rosenthal and others; Stickney and Watkins; Thorn and others). Re-treatment with corticotropin or cortisone may cause a second response in many cases, thus prolonging life in persons with acute leukemia (M. C. Rosenthal and others), but increasing resistance seems to occur with each course of therapy (Blood Club; Donohue and others; Earle and others; Pearson and Eliel; Pearson and others, 1949, 1950; Proceedings of First Clinical ACTH Conference; M. C. Rosenthal and others; Schulman; Spies and others; Stickney and Watkins). Oral maintenance therapy with cortisone appears to be practical and beneficial in the diseases of longer duration, such as chronic lymphatic leukemia, lymphosarcoma, and Hodgkin's disease (M. C. Rosenthal and others). It is significant that some patients whose leukemia has become refractory to treatment with "aminopterin" (4-aminopteroylglutamic acid) or urethan respond well to hormonal therapy, indicating different mechanisms of action (Blood Club; Dameshek and others; Pearson and Eliel; Pearson and others, 1950; Proceedings of First Clinical ACTH Conference; M. C. Rosenthal and others). There was no improvement in response when "aminopterin" and cortisone were used together in a few patients (Bell and Thomson; Cortisone Investigator), but further trials are indicated, since the myelostimulatory effects of corticotropin or cortisone might prevent the disadvantages of the myelosuppressive antifolic acid, mustard, and urethan compounds (M. C. Rosenthal and others). An estimate of the comparative value of corticotropin and cortisone is not possible at this time because of the relatively small number of patients treated and the need for a specific determination of the optimal dose of each hormone.

There is some suggestive evidence that corticotropin or cortisone may increase the catabolism of neoplastic tissue over that of normal tissue, and thus produce regression of the tumor (Pearson and others, 1949, 1950; Proceedings of First Clinical ACTH Conference; Thorn and others). However, histological examination of leukemic nodes (S. G. Taylor and others, 1950), leukemia cutis (M. C. Rosenthal and others), Hodgkin's disease nodes (Stickney and Watkins), and lymphosarcoma tissue (Spies and others) in several cases revealed no apparent changes after therapy. Nevertheless, a follicular lymphosarcoma showed definite disappearance of germinal centers with decreased cellularity (Pearson and others, 1949, 1950), and repeated biopsy specimens revealed improvement in the skin lesions of a patient with mycosis fungoides (S. G. Taylor and others, 1950). Further studies are indicated to determine the mechanism by which regression of the lymphoma is produced.

Estrogen administration, as an adjunct to corticotropin or cortisone therapy, might conceivably have some beneficial result by increasing endogenous corticotropin or by its own specific effect, as noted in animal experiments (Burrows, 1936, 1945; Gardner and others, 1944; Heilman and Kendall). Administration of

estrogen alone did not improve three patients with Hodgkin's disease and one each with chronic myeloid and lymphocytic leukemia (Haddow and others). Testosterone administration did not produce a beneficial response in a patient with lymphocytic leukemia (Astwood and others; Dameshek and others).

4. *Side-Effects.*—Undesirable side-effects were noted more frequently with corticotropin than with cortisone therapy. Higher doses resulted in a greater incidence of side-effects (S. G. Taylor and others, 1950).

a. Electrolyte Disturbances: After two weeks of therapy, most patients noted a progressive muscular weakness and easy fatigability (Pearson and others, 1949; Thorn and others). These were frequently due to a loss of serum potassium, since electrocardiographic changes of hypokalemia were noted in some of these patients. Oral administration of potassium chloride, 3 to 6 gm. per day, prevented and ameliorated these symptoms (Pearson and Eliel).

Retention of sodium and water is more commonly seen with corticotropin than with cortisone treatment. Weight gain and edema can result, with an increase in blood pressure (Pearson and Eliel; M. C. Rosenthal and others; Spies and others; S. G. Taylor and others, 1950). Care must be exercised to prevent the onset of congestive heart failure (Donohue and others; S. G. Taylor and others, 1950; Thorn and others). Marked diuresis, with disappearance of edema, usually occurs within two or three days of halting therapy (Pearson and others, 1949). Use of a salt-free diet and mercurial diuretics frequently can control the tendency toward edema formation (Pearson and Eliel; Pearson and others, 1950). Prolonged administration induces a negative balance of potassium, phosphorus, calcium, nitrogen, and chloride and a positive sodium balance, perhaps resulting in a hypokalemic, hypochloremic alkalosis (Pearson and Eliel; Proceedings of First Clinical ACTH Conference; Thorn and others). Supplemental administration of potassium is frequently utilized to counteract these disturbances (Pearson and Eliel).

b. Gluconeogenesis: There was an increase in the fasting blood sugar in most patients treated, and occasionally frank diabetes mellitus resulted (Pearson and Eliel; Pearson and others, 1949; M. C. Rosenthal and others; S. G. Taylor and others, 1950). These cases usually reverted to normal after therapy was discontinued (M. C. Rosenthal and others; Thorn and others). In diabetic patients, the insulin requirement for adequate control was increased by corticotropin or cortisone therapy (Thorn and others).

c. Cushing's Syndrome: With the corticotropin stimulation, there was an increased output of adrenal cortical hormones, which occasionally gave rise to a typical Cushing's syndrome picture (Albright; Pearson and Eliel; S. G. Taylor and others, 1950; Thorn and others). Furthermore, if adrenal androgen was also increased, there were associated acne, hirsutism, amenorrhea, and loss of scalp hair (Pearson and others, 1949; M. C. Rosenthal and others; S. G. Taylor and others, 1950). Catabolism of muscle tissue may produce muscular weakness (S. G. Taylor and others, 1950). The latter effect may be eliminated by the concurrent use of testosterone (Albright; Pearson and Eliel; Schilling and others; Sprague). Several weeks after halting treatment there was usually complete reversion of such side-effects (Proceedings of First Clinical ACTH Conference; Thorn and others).

d. Psychic Changes: Euphoria may occur because of direct changes in the central nervous system, as well as subjective improvement. Occasionally, psychosis

resulted, particularly when a personality disturbance had been present previously. This disturbance requires cessation of therapy and may or may not revert after treatment ceases (Pearson and Eliel; Proceedings of First Clinical ACTH Conference; M. C. Rosenthal and others; Spies and others; S. G. Taylor and others, 1950; Thorn and others). Rarely, convulsions may occur as a side-effect (Astwood and others; M. C. Rosenthal and others; Sprague).

e. Miscellaneous Side-Effects: Occasionally abdominal cramps and generalized pallor resulted from corticotropin administration because of use of a preparation that was contaminated with some posterior pituitary hormones (Thorn and others).

Pigmentation of the skin and nails was noted at times with both corticotropin and cortisone treatment. Sensitivity symptoms of fever, dermatitis, and arthritis were infrequently seen because the 11,17-oxysteroids interfere with allergic reactions (Thorn and others). Rarely, a first attack of gout was precipitated after corticotropin therapy was withdrawn (Proceedings of First Clinical ACTH Conference). In addition, gastrointestinal ulceration and hemorrhage, thromboembolic phenomena, azotemia, and a decreased resistance to pyogenic infection on occasion complicated therapy with either hormone (Blood Club; Pearson and Eliel; M. C. Rosenthal and others; Sprague; S. G. Taylor and others, 1950).

5. *Summary.*—Temporary remissions have been produced in some lymphomas by administration of corticotropin or cortisone. Further studies are needed to reveal their true value and mechanism of action in these neoplasms, but the fact that such a hopeless disease as leukemia can be temporarily halted should provide a greater stimulus for the chemotherapeutic approach.

F. Other Cancers

1. *Bladder Cancer.*—Carcinoma of the bladder has an average annual incidence of 5 to 6 cases in females and 11 to 12 cases in males per 100,000 population (Ackerman and del Regato; Dorn). The incidence is about the same in both sexes up to 50 years of age (Dorn), after which the disease occurs three times more commonly in males (Ackerman and del Regato; Huggins and Johnson), possibly indicating an endocrine dyscrasia in pathogenesis. The average duration of life is about 19 months in the untreated patient, although occasionally a patient with multiple papillary bladder carcinoma may survive 20 to 30 years (Huggins and Johnson). Therefore, results of treatment must be interpreted cautiously. There are about 3.2 living persons with the disease for each one who dies of the neoplasm (Ackerman and del Regato). The prime methods of cure are surgical treatment, fulguration, and irradiation, but a five-year survival rate of only 24 to 45% is obtained (Ackerman and del Regato). Palliation or additional methods of treatment would be of definite advantage in this disease.

The causation of bladder neoplasms is obscure. There is a high incidence among aniline-dye workers, with the carcinoma appearing 6 to 20 years after exposure. Since most patients do not have this type of exposure, it is possible that another carcinogen, excreted in the urine, may be involved (Huggins and Johnson). The close embryologic origin of the bladder and prostate has prompted therapeutic attempts with antiandrogenic measures, in the hope of producing benefits similar to those obtained in treatment of prostatic carcinoma (Lich and Grant). Marked alleviation of subjective symptoms and apparent retardation in the rate of tumor growth were noted after orchiectomy in two patients (Shivers).

Estrogen therapy has been used with some clinical and objective improvement in a number of other cases (Haddow and others; Haines and Miceli; Herbst, 1945; Huggins and Johnson; Lich and Grant). Diethylstilbestrol, 5 to 10 mg. per day (Haines and Miceli; Herbst, 1945), and triphenylchloroethylene, 3 to 6 mg. per day (Haddow and others), have been tried with clinical improvement in 14 of 23 cases. The most consistent effect has been the relief of vesical irritability, with marked lessening of dysuria, frequency, pain, and hematuria (Haines and Miceli; Lich and Grant), as well as control of bone metastases (Herbst, 1945). Regression of the primary tumor was also frequently noted on cystoscopy (Haddow and others; Haines and Miceli; Herbst, 1945; Lich and Grant). Biopsy has revealed changes in the bladder cancer cell that are similar to those noted in prostatic carcinoma cells after estrogen treatment (Haddow and others; Lich and Grant). However, viable tumor cells still remain in the bladder after the primary tumor has disappeared (Haddow and others), indicating that further treatment is necessary. In two cases, multiple papillomata were destroyed, thus allowing for a final cure by surgical or radium therapy which otherwise would not have been possible (Lich and Grant).

TABLE 14.—*Estrogen Treatment of Bladder Cancer*

Author	No. of Cases	Results	Comment
Haines and Miceli	7 M 3 F	6 males had marked symptomatic and objective improvement	Females not improved
Haddow and others.....	1	Subjective and objective improvement	Necrosis of tumor cells with primary tumor disappearance
Herbst, 1945	1	Good control of primary tumor and bone metastases	Radiation used also
Lich and Grant.....	11	1 improved clinically; papillomata disappeared	Low-grade cancers responded best

The response to estrogen treatment is influenced by several factors. Estrogen therapy appears to be more effective in the better differentiated tumors of Grades I and II, and particularly in the papilloma type (Haines and Miceli; Lich and Grant). The most malignant, undifferentiated bladder neoplasms are less responsive (Lich and Grant). Furthermore, males show better clinical and objective improvement with estrogen therapy than do females (Haines and Miceli). These observations indicate that physiologic endocrine processes may be involved in the therapy. Furthermore, the favorable preliminary clinical reports suggest the value of estrogen therapy in the palliation of bladder cancer, and further studies are indicated.

2. *Testicular Tumors.*—Cancer of the testis comprises less than 1% of all malignant tumors (Ackerman and del Regato). However, the testes are the commonest site of cancer in males of the 35 to 39 age group (Ackerman and del Regato; Nathanson, 1944 *a*; Twombly, 1948).

a. Non-Steroid-Hormone-Producing Tumors: The two primary types of testicular cancer are the seminoma, similar to the disgerminoma in females, and the teratoma. They do not produce hormones, except that the chorioepitheliomas (choriocarcinomas) of the teratoma group excrete chorionic gonadotropin and small amounts of estrogen and/or progesterone. Since these tumors arise during the

active sex life of the patient, an endocrine factor may be involved in their evolution (Endocrine-Cancer Conference; Panel on Tumors; Twombly, 1948). Furthermore, in patients with seminomas there are excessive output of F. S. H. and decreased androgen levels, which may cause an abnormal endocrine balance in the testicular tissue and predispose to cancer production (Twombly, 1944, 1948). A definite correlation of these neoplasms with ectopic testes has been noted, since cryptorchism exists in 11% of the recorded cases (Endocrine-Cancer Conference; Panel on Tumors; Twombly, 1948). In unilateral cryptorchids, the tumor was in the undescended testis in 97.5% of the cases (Endocrine-Cancer Conference). Perhaps the presence of an endocrine imbalance added to ectopia can produce the specific neoplastic change.

The prophylactic management of a patient with ectopic testis should include an attempt to place the testis in the scrotum by hormonal or surgical means. If this is not possible, a restoration of the hormone balance by administration of small amounts of estrogen and androgen conceivably could prevent the abnormally increased production of F. S. H. In patients with cancer of one testis, there is a good possibility that cancer may appear subsequently in the other testis, since a second tumor has been noted in 30% of undescended and 15% of scrotal testes, despite the usually rapid course of the disease (Endocrine-Cancer Conference). Again, prophylactic therapy, as indicated above, might be feasible in the seminoma type.

The treatment of these tumors is primarily by surgical procedure and irradiation (Ackerman and del Regato). However, palliation of the advanced metastatic case by hormone therapy has been suggested (Twombly, 1948). Teratomas often excrete large amounts of chorionic gonadotropin (Nathanson, 1944 *a*; Panel on Tumors; Twombly, 1948), having an L. H. action, and metastasize early with a rapid progression to death (Ackerman and del Regato; Panel on Tumors). Injections of serum from pregnant women had no beneficial effect (Twombly, 1948; Twombly and Hocker). Since estrogen produces testicular atrophy and its administration had a beneficial effect in a patient with uterine chorioepithelioma (Kullander), two patients with testicular chorioepithelioma were treated with large doses, but no apparent response was noted (Twombly, 1948). Perhaps progesterone would be more successful, since it has an L. H.-inhibiting effect that could decrease the output of chorionic gonadotropin and thus might affect the tumor. Seminomas are frequently characterized by an excessive F. S. H. output, produced by the pituitary (Endocrine-Cancer Conference; Panel on Tumors). Perhaps estrogen administration would have palliative value in these tumors, by means of its action in producing tubular atrophy and F. S. H. inhibition. There was a report describing beneficial effects of testosterone therapy in a case of disgerminoma (Russo and Kalso), showing that androgen therapy might be of aid in the analogous seminoma. Therapy with corticotropin, and therefore adrenal corticoids, had no beneficial effect in a case of testicular teratoma (Pearson and others, 1950).

b. Steroid-Hormone-Producing Tumors: Interstitial cell tumors are rare in man, accounting for 1% of all testicular neoplasms. They elaborate androgens, causing precocious puberty in young boys and possible increase of the 17-ketosteroid level in boys and adults (Kenyon; Twombly, 1948). They are quite common in aged dogs but rare in mice (Twombly, 1944, 1948). However, injection of

natural and synthetic estrogens produced these tumors in several strains of mice (Bonser and Robson; Endocrine-Cancer Conference; Gardner, 1943, 1944, 1945, 1948; Hooker and Pfeiffer; Panel on Tumors; Shimkin and others; Twombly, 1944, 1948). The transition to malignant growth included destruction of Leydig cells, with later production of neoplastic cells from the mesenchymal elements (Hooker and Pfeiffer). These new cells had metastatic ability and androgenic activity (Gardner, 1945; Hooker and Pfeiffer; Nathanson, 1944*a*). However, the tumors were strain- and species-limited (Endocrine-Cancer Conference; Gardner, 1943, 1944, 1945; Nathanson, 1944*a*), and foster nursing had no effect on the incidence (Endocrine-Cancer Conference; Shimkin and others). They were transplantable only in estrogen-treated animals of the susceptible strain. However, once it began, growth continued despite the cessation of estrogen administration or hypophysectomy, but no metastases occurred (Gardner, 1945, 1948). Simultaneous testosterone injections retarded the rate of growth but did not prevent these tumors from occurring (Hooker and Pfeiffer; Nathanson, 1944*a*). It is uncertain whether the estrogens act directly on the cells, as do carcinogenic hydrocarbons, or indirectly by means of pituitary L. H. stimulation (Panel on Tumors). The evidence favors the latter explanation since (1) the tumors produced are unlike those that follow hydrocarbon application (Panel on Tumors); (2) estrogens of differing chemical structure produce similar effects (Hooker and Pfeiffer); (3) transplantation of testes into the spleen of castrated males of susceptible strains produced Leydig-cell, mixed, and teratomatous tumors (Twombly, 1944). Endogenous androgen was inactivated by the liver, allowing for a chronic stimulation of the transplant by pituitary gonadotropins. The genetic susceptibility of these strains may be based on a specific sensitivity of the testis to chronic gonadotropin stimulation (Gardner, 1948) and further strengthens the view that the anterior lobe of the pituitary may be involved in the pathogenesis of testicular tumors (Hooker and Pfeiffer).

Estrogen-producing Sertoli-cell tumors are extremely rare in males (Berthrong and others; Teilum). These tumors are analogous to the granulosa-cell tumors of the ovary and are associated with a feminizing effect and an increase in estrogen excretion, which aid in diagnosis (Best and Taylor; Murray, 1937; Nesbit and others). They have also been noted to occur spontaneously in the dog (Huggins and Moulder).

The steroid-hormone-producing tumors of the testis are so rare that no palliative therapy has been recommended. Testosterone administration might retard the Leydig-cell tumors, as suggested by animal experiments (Burrows, 1945; Hooker and Pfeiffer; Nathanson, 1944*a*), possibly by L. H. inhibition. It could also be of value in reversing the feminizing influence of Sertoli-cell tumors. Surgical removal is recommended as the best method for achieving a cure.

3. *Cancer of the Adrenal Cortex.*—Adrenal cortical cancer is rare in animals and human beings. Tumors varying from adrenal hyperplasia to carcinoma have been produced in mice by castration before 2 months of age (Dorfman and Gardner; Nathanson, 1944*a*; Woolley; Woolley and Little; Woolley and others, 1939, 1940). This property was strain-limited (Endocrine-Cancer Conference; Gardner, 1948). All the cancers originated in the outer zone of the cortex within areas of previous hyperplasia and metastasized and had transplantability (American Association for Cancer Research, 1946; Endocrine-Cancer Conference; Gardner, 1948). Feminiza-

tion was noted in animals with marked cortical hyperplasia, (Gardner, 1941*a*), while masculinization followed the change to carcinoma (Endocrine-Cancer Conference; Nathanson, 1944*a*). The adrenal glands appeared to compensate for the gonadal insufficiency by increasing their sex-hormone output (Dorfman and Gardner; Gardner, 1941*a*, 1948; Woolley and Little). This mechanism may be mediated through a release of inhibition of the gonadotropin and corticotropin output subsequent to sex-hormone removal. Androgen or estrogen administration prevented these adrenal cortical changes (American Association for Cancer Research, 1946; Gardner, 1948).

Adrenal carcinoma in human beings may produce excessive amounts of sex hormones, as well as adrenal corticoids (Cahill; Frank; Kenyon; Kepler and Mason). The endocrine syndromes noted included signs of masculinization, or more rarely feminism, and metabolic derangements in both sexes (Burrows, 1945; Cahill; Frank; Kenyon; Parkes). Urinary excretion studies often revealed increased amounts of estrogens and certain ketosteroids, some of which might have been abnormal, thus providing an aid to early diagnosis (Burrows, 1945; Cahill; Dobriner and others, 1943, 1944, 1947; Endocrine-Cancer Conference; Frank; Fraser and others; Hirschmann and Hirschmann; Kenyon; Kepler and Mason; Parkes; Pincus and Thimann; Reifenstein and others; F. L. Warren).

Surgical removal of adrenal carcinoma will produce a cure, provided the diagnosis is made before metastases have occurred. Palliative therapy of the metastatic case could include the use of the steroid hormones which inhibit corticotropin production (Burrows, 1945; Cahill), such as testosterone, progesterone, adrenal cortical extract, or purified adrenal corticoids (cortisone and 17-hydroxycorticosterone [compounds E and F]). Furthermore, testosterone has been shown to supply the necessary anabolic stimulus that is lacking in Cushing's syndrome (Albright; Kenyon) and, thus, would be of aid in treatment of the type of adrenal carcinoma manifested by this picture. A patient with adrenal carcinoma treated with corticotropin did not have any objective benefits from therapy (Pearson and others, 1950).

4. *Pituitary Tumors.*—Tumors of the pituitary gland are not considered to be malignant, but their crucial site of origin and their relationship to steroid hormones suggest their inclusion in this review.

a. Experimental Studies: Pituitary tumors seldom occur spontaneously in mice or rats (Nathanson, 1944*a*; Saxton and Graham). However, after continued estrogen administration chromophobe adenomas have been produced in both sexes of several strains and their hybrids (American Association for Cancer Research, 1946; Cramer and Horning; Endocrine-Cancer Conference; Gardner, 1941*c*, 1944, 1948; Selye; Zondek). These tumors could be transplanted into estrogen-treated hosts, but not into untreated animals, indicating that the degree of autonomy is low (Gardner, 1944, 1948; Nathanson, 1944*a*). Synthetic and natural estrogens were equally effective (Endocrine-Cancer Conference), and there was no selective absorption of radioactive diethylstilbestrol by the pituitary (Twombly and Schoenewaldt), which shows that the physiologic inhibition of gonadotropin may be involved. These tumors do not excrete hormones. Simultaneous androgen administration decreased the incidence of tumor production (Gardner, 1948). Basophilic tumors have been found in castrated mice that had adrenal cortical carcinoma (Dickie and Woolley). It is possible that the abnormal adrenal gland can secrete excessive or unusual hormones that react on the pituitary to produce these tumors (Selye).

b. Human Studies: In man, the pituitary gland is larger in the female than in the male, and it enlarges still further during pregnancy with the increased amount of circulating hormones (Gardner, 1948). A chromophobe adenoma was noted in 1 of 12 patients who had died of breast carcinoma (Steiner and Dunham), suggesting a possible estrogen factor in the evolution of this tumor. Basophilic adenomas are frequently related to an adrenal hyperplasia or tumor, as noted in Cushing's syndrome (Albright). Symptomatic and objective improvement was noted with testosterone therapy in a patient with chromophobe adenoma (Posner) and in patients with the basophilic type (Albright). The mechanism of action of androgen in these cases, aside from the anabolic systemic effects, could be neutralization of an estrogen effect in the former or inhibition of adrenal corticoid output by decreasing corticotropin production in the latter. Further investigation of the testosterone action in these tumors is needed.

5. *Miscellaneous.*—Clinical attempts at palliative therapy with steroid hormones have been extended to include other cancers, mainly on an empirical basis.

a. Estrogen Therapy: Osteogenic tumors in one strain of mice were found to be three times as frequent in females as in males (Pybus and Miller, 1938*a*). Estrogen injections increased the incidence in males and decreased the age at which the tumors appeared in both sexes (Pybus and Miller, 1938*b*, 1940). Nevertheless, estrogen therapy appeared to enhance the effectiveness of irradiation therapy in two cases of osteogenic sarcoma (Binnie, 1942).

Questionable temporary alleviation of symptoms on estrogen administration was noted in a few cases of stomach and colon carcinoma and hypernephroma (Huggins, 1949), but no apparent response was obtained in cases of skin, maxillary antrum, rectal, or reticuloendothelial neoplasms (Haddow and others).

Estrogenic treatment produced a marked regression of lung metastases in a case of metastatic endothelioma (Roberts).

The pigmented nevus is quite sensitive to hormonal influence, as seen in the frequent increase in size and pigmentation with occasional malignant degeneration observed during pubescence and pregnancy (Pack and Scharnagel). Since castrated males do not elaborate melanin in their skin, castration was performed in several cases of generalized melanomatosis without beneficial effect (Howes; Pack and Scharnagel), although there is one report of improvement in a male (Herbst, 1942*b*). Estrogenic therapy would probably be of no value in malignant melanoma and might conceivably increase the rate of dissemination, as noted in pregnancy (Pack and Scharnagel).

b. Androgen Therapy: Testosterone administration in mice produced regression of a primary epithelioma, with a decreased incidence of metastases (Murlin and others). Testosterone may be administered to some patients with advanced metastatic carcinoma for its anabolic value. The tissue proteins were improved in three patients with advanced gastric carcinoma by administration of testosterone propionate, 50 mg. per day (Abels and others). A patient with leiomyosarcoma was treated with 2.25 gm. of testosterone given in 45 days. A positive nitrogen balance was produced, but no objective changes were noted (Schilling and others). Such anabolic effects may produce a temporary increase in strength, weight, and

well-being. Female patients with generalized melanomatosis were treated with castration or large doses of testosterone without any beneficial results (Pack and Scharnagel).

c. Adrenal Corticoid Therapy: Adrenal tissue was shown to have a retarding action on the growth of sarcoma grafts in rats (Lewis and others). Carruthers observed an inhibitory effect with cortisone therapy on a rhabdomyosarcoma in mice, but corticotropin had no effect (Cortisone Investigator). Marked alleviation of symptoms with some objective improvement was temporarily produced in two patients with squamous-cell carcinoma treated with cortisone, 150 mg. per day (Spies and others), and in one patient each having squamous-cell carcinoma (Spies and others) and tracheal carcinoma (S. G. Taylor and others, 1950) treated with corticotropin, 100 to 150 mg. per day. These effects were probably due to reduction in local edema, since biopsy revealed no change in the cancer (Proceedings of First Clinical ACTH Conference; Spies and others; S. G. Taylor and others, 1950). No objective beneficial effects were noted in six cases of gastric carcinoma, two cases each of Ewing's sarcoma, lung carcinoma, and malignant melanoma, and one case each of esophageal, gall-bladder, rectal, and colon carcinoma, osteogenic and synovial sarcoma, rhabdomyosarcoma, neuroblastoma, neurofibrosarcoma, angioendothelioma, and hypernephroma (Pearson and others, 1950; Postlethwaite and others; S. G. Taylor and others, 1950). However, most of the patients had some temporary symptomatic benefits, such as an increase in appetite and sense of well-being (Pearson and others, 1950; Proceedings of First Clinical ACTH Conference; Spies and others; S. G. Taylor and others; 1950).

The fractionation and identification of steroid-hormone products in the urine of normal and cancerous patients have aroused interest in the past few years (American Association for Cancer Research, 1949; Dobriner and others, 1943, 1944, 1947; Fraser and others; Lieberman and others; Reifenstein and others; Thorn and others). In patients with neoplastic disease, the excretion of adrenal cortical metabolites was markedly decreased, and often certain steroids were no longer demonstrable, or abnormal ones, such as 11-hydroxy-etiocholanolone, appeared (American Association for Cancer Research; Reifenstein and others; Thorn and others). Studies revealed a partial dysfunction of the adrenal cortex in patients with gastric cancer (Reifenstein and others). Therefore, adrenal function may be involved in the course of the malignant disease. The administration of corticotropin did not correct this metabolic dysfunction (Proceedings of First Clinical ACTH Conference; Thorn and others). Further investigations of this aspect of steroid-hormone metabolism may provide an adequate diagnostic test for early neoplastic change and may open new fields for steroid-hormone chemotherapy.

III. SUMMARY AND CONCLUSIONS

The intricate interrelationship of the endocrine glands, their hormones, and the organs affected is not understood completely as yet. However, some concepts of hormonal interaction are established and can be utilized in the rational selection of the proper hormone for therapy, according to the neoplastic organ involved.

The sex steroids and adrenal corticoids have systemic effects that are important in cellular metabolism. In general, the former are anabolic and the latter are catabolic. The steroid hormones also act upon electrolyte balance and enzyme

systems within the body. These generalized effects are involved in the response of the host to therapy, and further studies may emphasize these biochemical alterations on the normal and neoplastic cell metabolism.

Experimental animal investigations have been of value as a testing ground for the development of many concepts in steroid-hormone therapy. These basic studies will continue to offer a firm background for the clinical research of the future and provide the clinician with new methods of treatment.

The steroid hormones have definite value in producing temporary palliative benefits in several types of cancer. In some cases, the relief of suffering is dramatic and a prolongation of useful life is effected. Since steroids have been shown to influence the progression or regression of some neoplasms, it is hoped that pro-

TABLE 15.—*Value of Steroid Hormones in Treatment of Cancer*

Site or Type of Neoplasm	Definite Effect	Possible or Theoretical Effect		Adjunct to Surgical Measures or Irradiation
		Prophylactic	Treatment	
A. Female breast	Testosterone; estrogen	Testosterone; progesterone	Progesterone	Testosterone; estrogen
B. Male breast	Estrogen	.....	.....	Estrogen
C. Prostate	Estrogen	Progesterone	Progesterone	Estrogen
D. Pelvic	.....	Testosterone; progesterone	Testosterone; progesterone	.....
E. Lymphoma	Adrenal corticoids	.....	Estrogen added to adrenal corticoids	.....
F. Other neoplasms				
Bladder	.....	.....	Estrogen especially in males	Estrogen
Testes	.....	Testosterone; estrogen	Testosterone; estrogen	.....
Adrenal cortex	.....	.....	Testosterone; progesterone; adrenal corticoids	.....
Pituitary	.....	.....	Testosterone; progesterone; adrenal corticoids	.....
Miscellaneous	.....	.....	Testosterone; estrogen; adrenal corticoids	.....

phylactic therapy with the proper hormone may prevent the process of carcinogenesis. Furthermore, future studies may prove the value of adjunctive steroid chemotherapy in raising the cure rate of surgical or irradiation treatment.

The steroid hormones have diagnostic as well as therapeutic significance in cancer. Specifically, there is often an increase in the urinary excretion of the steroid metabolites in the following hormone-producing neoplasms:

1. Ovary
   (*a*) Granulosa-cell carcinoma
   (*b*) Arrhenoblastoma
   (*c*) Adrenocortical carcinoma
2. Testis
   (*a*) Interstitial-cell tumor
   (*b*) Sertoli-cell tumor
3. Adrenal cortex
   Adrenocortical carcinoma

Furthermore, there may be an abnormality in the qualitative excretion of the steroid metabolites in many types of cancer. Future investigation of this approach may produce the test for early diagnosis that is so needed in cancer control.

The necessity for further advances in the treatment of cancer is one of the most important problems in medicine today. It is apparent that surgical treatment and irradiation, for practical purposes, have reached their maximum of effectiveness but do not offer the final answer in many cases. Chemotherapy may be the necessary approach for further success in this field. In particular, the steroid hormones have demonstrated a definite action in the stimulation and inhibition of many neoplasms. This is of special significance, since these substances are found normally in the body. Future investigation of the endocrine balance in the host may reveal the biochemical changes important in the pathogenesis, prophylaxis, diagnosis, and treatment of certain malignant growths.

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News and Comment

GENERAL NEWS

American Trudeau Society
Medical Section of the National Tuberculosis Association

CURRENT STATUS OF ISONICOTINIC ACID HYDRAZIDE IN THE TREATMENT OF TUBERCULOSIS

The Executive Committee of the American Trudeau Society has reviewed the available evidence on the antituberculous activity of isonicotinic acid hydrazide as presented by Hoffmann-La Roche, Inc., E. R. Squibb & Sons, and investigators cooperating with them. On the basis of this evidence, the Committee makes the following statement for the guidance of the medical profession:

1. *Chemical Structure:* Isonicotinic acid hydrazide ("nydrazid," trade name of E. R. Squibb & Sons; "rimifon," trade name of Hoffmann-LaRoche, Inc.) is a chemically pure, synthetically produced substance of the general formula $C_6H_7N_3O$.

It is obtained in almost colorless crystals which are highly soluble in water. A closely related derivative, which is also being studied for its antituberculous properties, is the isopropyl derivative ("marsilid," trade name of Hoffmann-La Roche, Inc.).

Isonicotinic acid hydrazide is also related to pyrazinamide ("aldinamide," trade name of Lederle Laboratories) and to amithiozone ("tibione," trade name of Schenley Laboratories).

2. *Activity in Vitro:* Isonicotinic acid hydrazide is bacteriostatic in vitro against M. tuberculosis H37Rv in a concentration as low as 0.02 to 0.06 γ/ml. It apparently has a very narrow antibacterial spectrum, being ineffective in vitro against the common Gram-negative and Gram-positive pathogenic bacteria, against certain protozoa, and against the influenza virus in mice. It may possess some slight antifungal properties.

3. *Activity in Vivo:* In several species of experimental animals (mice, guinea pigs, rabbits, and monkeys), experiments on the effectiveness of isonicotinic acid hydrazide against tuberculous infection with virulent human strains of M. tuberculosis have given promising results in arresting the course of the experimentally produced disease. On the basis of these observations, isonicotinic acid hydrazide appears to be approximately the therapeutic equivalent of streptomycin, at least in the first few months of treatment. Observations on the emergence of strains of tubercle bacilli which may be resistant to isonicotinic acid hydrazide, either in vitro or in vivo, are meager, and it is not known if such strains will emerge during treatment or if such emergence will have therapeutic significance. A definite increase in resistance has been obtained in vitro with one strain (BCG).

4. *Toxicity and Pharmacology:* Although the toxicity of isonicotinic acid hydrazide has been determined fairly accurately in several species of animals, some aspects of the pharmacology and toxicology of the drug have not been completely elucidated. On the basis of available studies it appears that both isonicotinic acid hydrazide and its isopropyl derivative are of relatively low toxicity in dosage ranges which appear to be effective. The drugs are apparently largely excreted in the urine. Within an hour or so after administration they appear to be well distributed throughout the body (blood serum, cerebrospinal fluid, pleural fluid).

5. *Dosage:* On the basis of preliminary studies, the indicated daily dosage is in the range of 3-5 mg./kg. body weight (150-300 mg. per day for the average adult). This dosage is given by mouth in two or three divided doses. The drug may also be given parenterally.

6. *Toxicity in Man:* In the dosage range indicated, preliminary observations in man indicate that there is little significant or serious toxicity. The following have been observed but on a more or less transitory basis even though drug administration is continued:

a. Constipation

b. Difficulty in starting micturition (in males especially)

c. Increased reflexes

d. Positional hypotension and dizziness

e. Eosinophilia (in about 10% of cases)

f. Slight drop (0.5-1.0 gm.) in hemoglobin concentration

g. Occasional casts and traces of albumin and reducing substances in the urine

Toxic effects on the eighth cranial nerve, impairment of renal or hepatic functions, or dermatologic manifestations associated with the drug have not been observed so far.

7. *Activity in Man:* Preliminary observations on the effect of isonicotinic acid hydrazide on the course of tuberculosis in man have been limited largely to patients with far-advanced pulmonary disease, extensive tissue destruction, positive sputum, and, as a rule, considerable symptomatology, many of whom have failed to respond or would not be expected to respond to other available therapy. In such patients, treated with 3-5 mg./kg./day for up to five months of therapy (the majority were treated for two to three months), the following changes in clinical course have been observed:

a. Reduction in fever, if present, in two to three weeks, in the majority

b. Reduction in cough, in the volume of sputum, and in the number of tubercle bacilli raised (as determined by smear); no information is available on conversion of the sputum as determined by culture

c. Gains in appetite, weight, and strength

d. Some clearing of the reversible component of the pulmonary tuberculous disease by x-ray observation

e. Initial favorable response in such nonpulmonary lesions as draining sinuses and fistulae and mucous membrane tuberculosis, and in a very few cases of miliary and meningeal tuberculosis

8. *Problems:* At the present time complete information is lacking on many aspects of the therapy of tuberculosis with isonicotinic acid hydrazide. Among the unknowns are the following:

a. The mechanism of action of the drug on the tubercle bacillus—whether it is tuberculocidal or tuberculostatic; the effect upon the enzyme chemistry of the tubercle bacillus, etc.

b. The mechanism of action upon the host—basically, the precise toxicity in man

c. The optimal dosage—the number of milligrams per day; whether it needs to be given every day; the optimal mode of administration

d. The duration of therapy—whether its effect is comparable with that of streptomycin and paraaminosalicylic acid (PAS), indicating relatively long courses of treatment, or whether shorter courses may be as effective

e. The rate of emergence of drug-resistant strains of tubercle bacilli

f. The effect of the drug upon the bacteriology of the patient—data are lacking on conversion of sputum by culture; the tissue bacteriology after varying amounts of treatment will need to be studied

g. The question of potential relapse after initial improvement

h. The question of whether basic systemic therapy of tuberculosis (especially bed rest) can be modified as a result of treatment with isonicotinic acid hydrazide

9. *Precautions:* At present there is no reason to believe that the fundamentals of therapy of tuberculosis should be altered in any way when isonicotinic acid hydrazide is employed. Patients receiving the drug should be hospitalized for careful observation. They should be studied in institutions where potential toxic manifestations may be watched for most carefully and where effects upon the course of the underlying tuberculosis may be carefully observed so that suitable alterations of therapy may be initiated when indicated. Routine laboratory precautions should include frequent blood counts and urinalyses, neurologic examinations, and tests for renal and hepatic insufficiency.

10. *In General:* The introduction of a new drug in the therapy of tuberculosis is likely to raise more questions for a few years than it will answer. There is no knowledge at the

present time that isonicotinic acid hydrazide or its isopropyl derivative will accomplish more than has been accomplished with streptomycin and PAS. It may prove to be an additional drug of great value. It may be years before its exact contribution to the therapy of tuberculosis can be assessed accurately. A large reservoir of undetected and untreated cases of active tuberculosis exists throughout the United States, and there is every expectation that, in spite of the more effective chemotherapy of tuberculosis currently available, the need for hospitalization in institutions with qualified personnel and adequate laboratory facilities will increase rather than decrease. There is at present no basis for expecting that isonicotinic acid hydrazide, or any other drug available, can safely be counted upon to reduce the duration of hospitalization. Rather, in most instances, at least, it may lead to prolongation of hospital treatment since effective chemotherapy may facilitate desirable forms of therapy not otherwise possible.

It should be emphasized strongly that, with more numerous effective antituberculous compounds available in the treatment of tuberculosis, more intensive case finding than ever will be indicated. Only through this means can maximum advantage be taken of improvements in therapy.

11. *Summary:* After a review of available data on the action of isonicotinic acid hydrazide and its isopropyl derivative upon the tubercle bacillus in vitro, and upon the course of experimental tuberculosis in animals and clinical tuberculosis in man, it may be stated that their demonstrated action, although highly encouraging, appears in no way to alter the basic principles of the treatment of tuberculosis as presently understood. Much more work will need to be done to ascertain the exact place of these drugs in the treatment of the disease. With several carefully coordinated studies in prospect, it is anticipated that further information will accumulate rapidly.

ANNOUNCEMENTS

Postgraduate Course in Psychiatry and Neurology.—A postgraduate course in psychiatry and neurology will be given from Aug. 25 through Oct. 31, 1952, at the Langley Porter Clinic, University of California School of Medicine, San Francisco. The courses are given by the Department of Psychiatry of the University in cooperation with the University Extension (Medical Extension) and will be under the direction of Dr. Karl M. Bowman. The course will be a general review of psychiatry and neurology, with material from related fields in medicine. It is particularly designed to prepare psychiatrists and neurologists for taking the examinations of the American Board of Psychiatry and Neurology. The fee for the course is $200. The fee, application, and biographical data on place of legal residence, medical school attended and year of graduation, and training and experience in psychiatry should be sent to Stacy R. Mettier, M.D., Professor of Medicine, Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22.

Postgraduate Symposium on Basic Sciences Related to Anesthesiology.—The Department of Surgery, Section of Anesthesiology, University of Pittsburgh School of Medicine, in cooperation with the Departments of Anesthesiology of the St. Francis, Allegheny General, and Mercy Hospitals, is giving a postgraduate symposium on the basic sciences related to anesthesiology, June 2 to 6, 1952. Further information may be obtained from the Chairman of the Committee on Graduate Medical Education, University of Pittsburgh School of Medicine, 3941 O'Hara St., Pittsburgh 13.

PERSONAL NEWS

Dr. G. Burroughs Mider.—The appointment of Dr. G. Burroughs Mider, of Rochester, N. Y., as Scientific Director at the National Cancer Institute of the National Institutes of Health was announced by Surgeon General Leonard A. Scheele of the Public Health Service, Federal Security Agency.

Dr. Mider is professor of cancer research and coordinator of cancer teaching in the School of Medicine and Dentistry at the University of Rochester.

Books

A Text Book of Medicine. Eighth edition. Edited by Russell L. Cecil and Robert F. Loeb. Price, $12. Pp. 1627, with 204 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1951.

The eighth edition of Cecil's text lives up to the high standard set by its predecessors. It contains the many revisions and additions of completely new material necessitated by the startling medical discoveries since the last edition in 1947. In the present text Dr. Robert F. Loeb acts as co-editor, and Dr. Alexander Gutman, Dr. Walsh McDermott, and Dr. Harold Wolff have been added as associate editors.

To the long list of distinguished contributors to past editions have been added names of new authors who speak with equal authority. The section on diseases of the adrenal glands by Dr. George W. Thorn is of particular interest because of the present intense investigation on corticotropin (ACTH) and cortisone. For the same reason, the section on "Diseases of Collagen," which has been expanded and regrouped, is of special significance. Such new subjects as vitamin B_{12} and folic acid deficiency, beryllium poisoning, rickettsial pox, and chronic amphetamine poisoning are discussed for the first time.

To its many old friends, "Cecil" needs no introduction, but even to them the eighth edition will be a pleasant surprise.

Transactions of the Seventh Conference on Cybernetics, New York, March 23-24, 1950. Edited by Heinz Von Foerster, Margaret Mead, and Hans Lukas Teuber. Price, $3.50. Pp. 251. Josiah Macy, Jr., Foundation, 565 Park Ave., New York 21, 1951.

Cybernetics is defined in a subtitle as "circular causal and feedback mechanisms in biological and social systems." The conference was made up of seven mathematicians and engineers, seven neuropsychiatrists, four psychologists, three biologists, and three from the social sciences—an able and articulate group! Seven of these presented material for discussion. R. W. Gerard talked on "Some of the Problems Concerning Digital Notions in the Central Nervous System." This paper is important to cybernetics, as defined. It deals with the difference between analogical systems, where continuous processes are measured, and digital systems, where discrete phenomena are counted. For example, in nystagmus it is a question whether one is dealing with repetitive activity of individual components or more continuous activity of reverberating circuits. In regard to the resemblance of the human brain to a calculating machine, Gerard wisely says: "To take what is learned from working with calculating machines and communication systems, and to explore the use of these insights in interpreting the action of the brain, is admirable; but to say, as the public press says, that therefore these machines are brains, and that our brains are nothing but calculating machines, is presumptuous. One might as well say that the telescope is an eye, or that a bulldozer is a muscle."

The remaining six papers are all on speech. Licklider discussed the manner in which, and extent to which, speech can be distorted and remain intelligible. This is an important problem in communication engineering. Shannon gives an interesting paper on redundancy in English, showing how much our language may be compressed by coding for transmission. Mead talked of her experience in learning primitive languages through the use of high-level linguistic abstractions. Without an interpreter she has been able to "crack" an unknown language because of her wide knowledge of linguistic possibilities and probabilities. Wermer describes an interesting series of experiments on children, which he carried out to determine the ages at which different sorts of meanings of words develop. Kubie made the already complicated picture of language more complex by bringing in the concepts of symbolization and repression. His thesis is that in speech we use a symbol for something of which we are conscious; in neurosis we use a symbol for something of which we are not aware. Neurosis is for him a maladjustment in human life that has its origin in the repressed unconscious. This point of view he ably upholds in a long discussion, but it is not a definition of neurosis as yet generally accepted.

Concerning the discussions reported verbatim and at length in the book, one can only say that it may later be of historical interest to know exactly what these gifted members of the conference said, but, from the standpoint of clear communication, much of it is a waste of time, and is distracting and confusing to impose on the reader (for example, on page 25, lines 12 to 24 are nonsense). Too much loose talk is immortalized by too-perfect recording machines!

Hypertension: A Symposium Held at the University of Minnesota on Sept. 18-20, 1950. Edited by E. T. Bell. Price, $7.50. Pp. 573, with illustrations. University of Minnesota Press, 10 Nicholson Hall, Minneapolis 14, 1951.

On Sept. 18 to 20, 1950, a symposium on hypertension was held at the University of Minnesota in honor of Dr. Elexious T. Bell, Dr. Benjamin J. Clawson, and Dr. George E. Fahr, each of whom holds the title of Professor Emeritus of the University of Minnesota Medical School. Distinguished clinicians and investigators from all parts of the United States contributed papers on the subject of hypertension, beginning with the history and progressing to discussions on the anatomy, etiology, pathology, pathophysiology, experimental production, symptomatology, and treatment of the various forms of hypertension.

This book comprises in chapter form all the papers given at the three-day meeting and includes the interesting floor discussions which followed the presentation of each paper.

The book represents a valuable addition to the library of both the physician whose primary interest is cardiovascular disease and the general physician as an excellent source of reference on all problems pertaining to hypertension.

Physical Diagnosis. By Raymond W. Brust, M.D., F.A.C.P. Introduction by Truman G. Schnabel, M.D., F.A.C.P. Price, $4.50. Pp. 294, with 60 illustrations. Appleton-Century-Crofts Company, Inc., 35 W. 32d St., New York 1, 1951.

In 294 pages this book covers concisely but thoroughly the art of the physical examination, and as such lends itself more to the use of the student and intern than to that of the practicing physician. In a well-outlined form it covers in proper sequence examination procedures of the various systems as they should be approached, beginning first with the body in general, and progressing to the head and neck and the pulmonary, cardiovascular, gastrointestinal, and nervous systems, in that order. The material is well presented and easy to interpret, and interest is further augmented by the occasional inclusion of abnormal physical findings in some of the commoner disorders of the particular system under discussion, and by the use of 60 well-chosen illustrations.

History-taking is briefly dealt with, but the laboratory, roentgenologic, electrocardiographic, and other special examinations are not mentioned.

Untoward Reactions of Cortisone and ACTH. By Vincent de Paul J. Derbes, M.D., and Thomas E. Weiss, M.D. Price, $2.25. Pp. 87, with 2 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1951.

Derbes and Weiss's book is another of the brief monographs included in the American Lecture Series; it deals with the untoward effects of cortisone and corticotropin (ACTH). The subject has become rather hackneyed, as many good reviews are already available, but this is an excellent summary written in simple terms.

The Medical Clinics of North America. Philadelphia Number. Symposium on Diagnosis in General Medicine. By various authors. Price, $2.50. Pp. 1577-1908, with illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, November, 1951.

This number of *The Medical Clinics of North America* is excellent. The articles are, of necessity, brief on any particular subject. However, they skillfully cover many of the newest diagnostic procedures and include good bibliographies to allow for detailed study of all procedures mentioned. The volume points the way to a sound, logical method of diagnosis in all fields covered. It can be highly recommended to all practitioners.

Conference on Problems of Consciousness: Transactions of the First Conference. Edited by Harold A. Abramson. Price, $3. Pp. 200. Josiah Macy, Jr., Foundation, 565 Park Ave., New York 21, 1951.

This monograph represents a "free exchange of ideas" concerning the problems of consciousness at the first conference sponsored by the Josiah Macy, Jr., Foundation, held on March 20 and 21, 1950, in New York. It contains the following chapters:

"The Sleep-Wakefulness Cycle," by Nathaniel Kleitman

"Psychoanalytic Concepts of Sleep and Dreams," by Gregory Zilboorg

"Perception of Pain and Some Factors That Modify It," by Henry K. Beecher

"The Phenomena of Hypnosis," by Margaret Brenman

"Consciousness and the Chemistry of Time," by Hudson Hoagland

To read through these extremely lively and interesting discussions on such a remarkably high level of "consciousness" of the participants is, indeed, a great pleasure. The book is highly recommended.

Reports of the Steno Memorial Hospital and the Nordisk Insulinlaboratorium. Volume IV. Edited by Axel M. Hemmingsen. No price given. Pp. 88. C. Hamburgers Bogtrykkeri A/S, Copenhagen, Denmark, 1950.

This is the fourth annual volume from the Steno Memorial Hospital. The contents are as follows:

"The Relation of Standard (Basal) Energy Metabolism to Total Fresh Weight of Living Organisms," by A. M. Hemmingsen

"Splitting of Energy-Rich Phosphate Bonds," by T. Rosenberg

"Clinical Vascular Symptoms in Patients with Juvenile Diabetes Mellitus After at Least 15 Years' Duration," by E. D. Bartels and J. E. Poulsen

"Insulin Allergy and Insulin Resistance," by M. V. Jarlov

A list of papers published from the Steno Memorial Hospital and Nordisk Insulinlaboratorium since the preceding list in Volume 1, 1946, but not appearing in these "Reports."

A dramatic conclusion resulting from Dr. Hemmingsen's contemplation of energy metabolism is that if a homothermal animal weighing 3 tons were to have the same standard energy metabolism per kilogram of body weight as a rat its surface temperature would have to be above the boiling point of water. The proportionality between the metabolic rate and body surface obviates this difficulty.

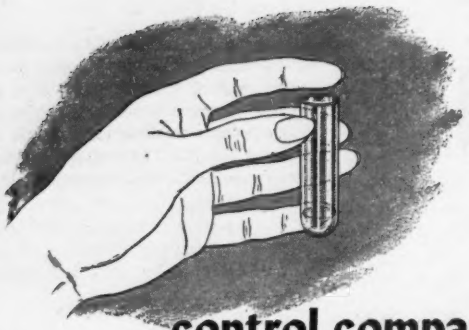
Bartels and Poulsen arrive at the same rather gloomy conclusions that have been reached by many American authors on the outlook for the diabetic child. Vascular lesions were found in about 50% of the 116 children with diabetes that had lasted more than 15 years; retinopathy, in 27%; proteinuria, in 27%, and hypertension, in 23%. The mortality rate was 16.7%.

The Specialties in General Practice. Edited by Russell L. Cecil, M.D. Price, $14.50. Pp. 818, with 470 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1951.

Dr. Cecil and fourteen distinguished specialists have compiled a book designed to help the general practitioner solve the special problems he sees. An effort is made to enable the practitioner to establish at least a tentative diagnosis and to institute the best possible therapy without delay. Adequate warnings are included which indicate when a consultation with a specialist is needed. A discussion on follow-up care after the patient has been treated by a specialist is included.

Obviously, in any attempt to cover fourteen specialties in one volume, only the major problems in each specialty can be considered, and these only briefly. This has been done with great clarity and skill. All theoretical discussion has been omitted, and only facts are presented. The many tables, illustrations, and charts greatly enhance the value of the book.

This volume should serve the general practitioner as a valuable handbook for diagnosis and treatment of specialized problems. It is, in addition, a good review of new methods and procedures. It is in no sense a textbook of the specialties.



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Sprague, R. G.: Cortisone and ACTH, Am. J. Med. *10*:567, 1951.

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